VOLUME 30 NUMBER 10 OCTOBER, 1947

AMERICAN JOURNAL OF OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

CONTENTS

		PAGE
Ectodermal framework of the optic nerve	*Henry C. Haden*	1205
Streptomycin in ophthalmology	*J. G. Bellows and C. J. Farmer*	1215
Technique of vitreous replacement	*Milo H. Fritz, Theresa M. Fennessy, and Hugo Cabrera*	1221
Bilateral uveitis from horse serum	*T. F. Schlaegel, Jr.*	1225
Stimulation of corneal epithelization	*Frank W. Newell*	1238
Effects of D.F.P. on rabbit eyes	*Ludwig von Sallmann and Beatrice Dillon*	1244
Transfer of ascorbic acid	*V. Everett Kinsey*	1262
A statistical study of glaucoma	*J. C. Holst*	1267
Diagnosis of early glaucoma	*Hendrie W. Grant*	1276
The dissatisfied refraction patient	*C. A. Veasey, Jr.*	1286
Bilateral ophthalmoplegia in poliomyelitis	*Edwin S. Wright*	1294
Restoration of human orbits	*M. Harvey Johnson*	1298
Blackboard cornea for teaching	*Andrew de Roetth, Sr.*	1299

DEPARTMENTS

Society Proceedings	1300
Editorials	1311
Book Reviews	1316
Correspondence	1318
Abstracts	1319
News Items	1342

For complete table of contents see advertising page XI

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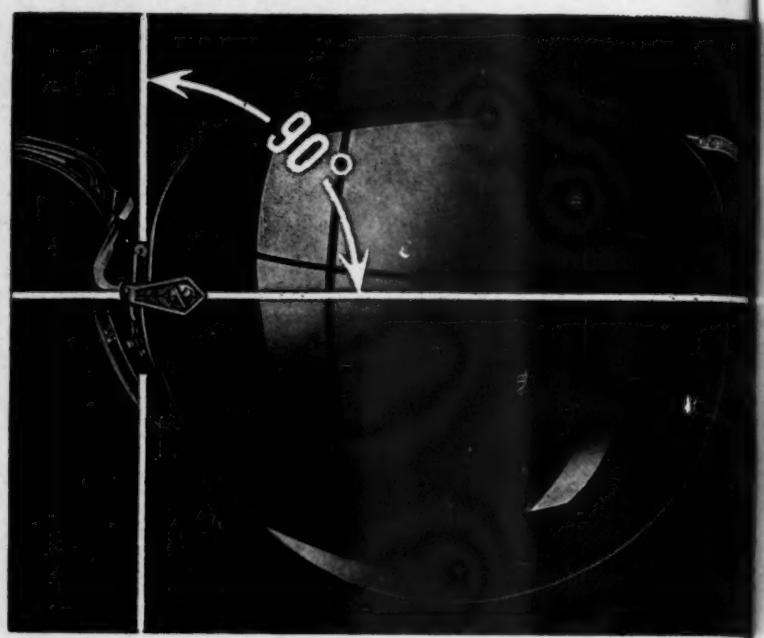

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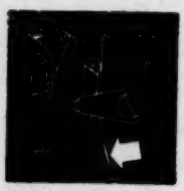

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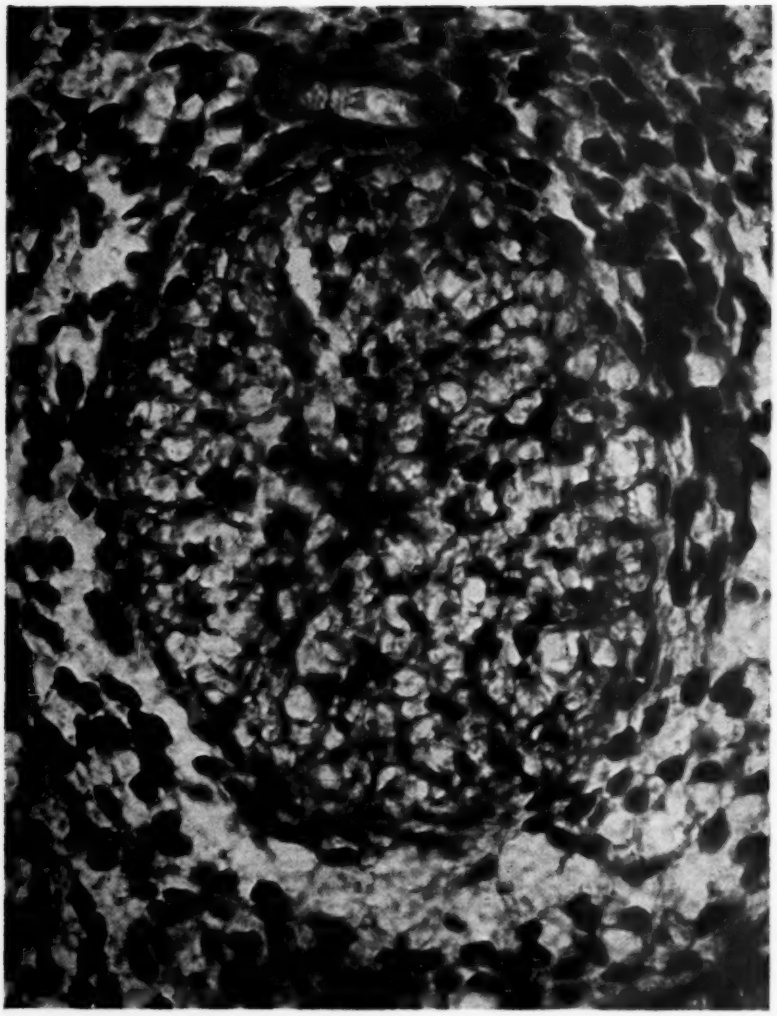

FRONTISPIECE (HADEN). CROSS SECTION OF OPTIC STALK SOON AFTER ENTRANCE OF AXONS OF GANGLION CELLS OF RETINA.

AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 30 OCTOBER, 1947 NUMBER 10

THE DEVELOPMENT OF THE ECTODERMAL FRAMEWORK OF THE OPTIC NERVE, WITH ESPECIAL REFERENCE TO THE GLIAL LAMINA CRIBROSA*

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Houston, Texas

When the optic stalk first appears, its wall is composed of undifferentiated epithelial cells (fig. 1) differing in no way from those of the optic vesicle and brain wall with which it is in continuity.

At about the 15-mm. age, the axons of the ganglion cells of the retina grow back into the wall of the optic stalk on their way to the brain, which they reach at the 20-mm. age. The entrance of the axons, the optic-nerve fibers, into the stalk wall initiates a great change in the epithelial cells of the stalk wall. Their nuclei become somewhat oval, and the cell protoplasm vacuolated and partially absorbed. The result is an irregular arrangement of starlike cells with anastomosing processes through which the optic-nerve fibers pass *(frontispiece)*. These are the glial cells which form the sustentacular tissue, framework, or septa of the optic nerve in young embryos.

At first the glial cells are scattered irregularly throughout the nerve, and the optic-nerve fibers passing among them are not in parallel rows. Later on the glial cells show a tendency to line up in longitudinal rows between the bundles of optic-nerve fibers to form the primary septa. In longitudinal sections of a 20-mm. embryo (fig. 2) the early condition is apparent. The optic-nerve fibers are not in bundles but course irregularly throughout the nerve, and the glial cells have no definite pattern (fig. 2).

Cross section of the fellow nerve of the 20-mm. embryo made back of the globe, near the entrance of the hyaloid artery, shows this lack of design (fig. 3) but about the middle of the orbital part of the nerve (fig. 4) the glial cells congregate about its axis in a stellate arrangement. In the posterior third of the nerve (fig. 5) the residual lumen of the optic stalk is seen with glial cells surrounding it. The cells forming its lining have the appearance of the original epithelial cells. If the lumen of the stalk is followed back (fig. 6) it will be found to pass into the recessus opticus in the telencephalon. At the 29-mm. age (fig. 7) longitudinal sections show more regularity of arrangement but the optic-nerve fibers are not in bundles and the glial cells are not lined up in parallel rows to form septa. Cross section of the fellow nerve of the 29-mm. embryo (fig. 8) in the region of the anlage of choroid shows more definite design. The cell bodies are more regularly spaced and the anastomosing processes form a network through

* Read at the 82nd annual meeting of the American Ophthalmological Society, San Francisco, California, June, 1946.

which the nerve fibers pass. The appearance is very much that of the definitive glial lamina cribrosa.

There is not much regularity of pattern of the nerve as a whole until the 45-mm. age is reached when some suggestion of rows of glial cells are seen (fig. 9). Also the peripheral glial mantle is well developed (fig. 9). It is recognized as a layer of cells continuous with the pigment layer of the retina. It leaves the pigment layer at almost a right angle and passes brainward, covering the outer surface of the optic nerve. As it is a continuation of the pigment layer of the retina, which is a modification of the original wall of the optic vesicle, the peripheral glial mantle must be composed of the original epithelial cells forming the outer surface of the stalk. Processes from it enter into the nerve but no mesodermal tissue other than that accompanying the hyaloid artery is found in the nerve at this age. At the end of the optic nerve adjacent to the vitreous there is a clumped mass of cells called "Bergmeister's Papilla" (fig. 9), the analogue of the pecten of birds. It is composed of original epithelial (ectodermal) cells which were isolated by the curving nerve fibers as they grew back from the inner wall of the optic cup into the stalk (fig. 9).

The nerve of the 67-mm. embryo (fig. 10) shows much more regularity of detail when seen in longitudinal section. The glial cells are lined up in parallel longitudinal rows between the bundles (fasiculi) of nerve fibers in the orbital portion. In the distal end of the nerve, that opposite the anlagen of the choroid and sclera, the arrangement is different. Here the glial cells lie in well-defined parallel rows with the long axes of their nuclei at right angles to the nerve fibers. These constitute the anlagen of the laminae cribrosae (fig. 10). Until the 67-mm. age, the optic nerve is composed of only ectodermal tissue with the exception of the mesoderm accompanying the hyaloid artery. At this age capillaries accompanied by fibroblasts grow into it from the anlage of the pial sheath. This is the first invasion of the mesoderm which is to grow along the columns of glial cells which form the primary septa of the nerve. From this age on the mesoderm grows into the nerve and follows the columns of glial cells as a grapevine climbs on an arbor. In this manner the mesoderm replaces most of the glial cells and forms the definitive fibrous connective-tissue septa of the optic nerve. However, there are always gaps in the mesodermal septa which are filled in by glial cells. By the 97-mm. age (fig. 11) there is much more mesoderm in the orbital portion of the nerve but there is none in the region opposite the choroid and sclera, the anlagen of the laminae cribrosae. Cross sections through this location show the glial cells and processes forming a network through which the nerve fibers pass. The appearance is very much as it was when the glial cells first formed.

At about 4½ months of age (fig. 12) a change takes place in the distal end of the nerve. Rows of glial cells from Bergmeister's Papilla grow out into the vitreous on either side of the hyaloid artery forming its glial sheath. There is a space between the sheath and the walls of the artery. This sheath disappears before birth. By the 360-mm. age (circa 7 months) many fibrous connective-tissue fibers have grown into the network of glial cells opposite the anterior third of the sclera to form the connective-tissue lamina cribrosa (lamina scleralis). They are a direct ingrowth from the sclera (or the border tissue, which is the same) and not a forward growth of the septa

of the orbital portion of the optic nerve. These mesodermal fibers increase in number until, at the 500-mm. age (fig. 13), they form the major portion of the scleral lamina cribrosa. The portion of the nerve anterior, or distal, to the lamina scleralis is not invaded by mesoderm at any time but remains ectodermal throughout life. Toward the end of fetal life, the nerve fibers in the orbital portion of the optic nerve are medulated, the medulation ceasing at the posterior, or brain side, of the lamina scleralis (connective-tissue lamina cribrosa). The nerve fibers anterior to the connective-tissue lamina cribrosa are naked axis cylinders. The glial cells and fibers that lie in front (fig. 14) of the lamina scleralis and opposite to the choroid form the glial lamina cribrosa, which is also called lamina chorioidalis (fig. 14).

The glial lamina cribrosa occupies a unique position for it is the framework of the optic disc (fig. 15) and the ophthalmoscopic picture varies with its arrangement. Furthermore, it participates in all pathologic processes involving the intraocular end of the optic nerve and it must be destroyed before the typical glaucomatous cup can be produced.

1914 Travis Street.

The illustrations which follow were made from unretouched photographs of sections of human embryos and fetuses in my private collection.

Fig. 1 (Haden). 4-mm. embryo, section of stalk wall. Undifferentiated epithelial cells.

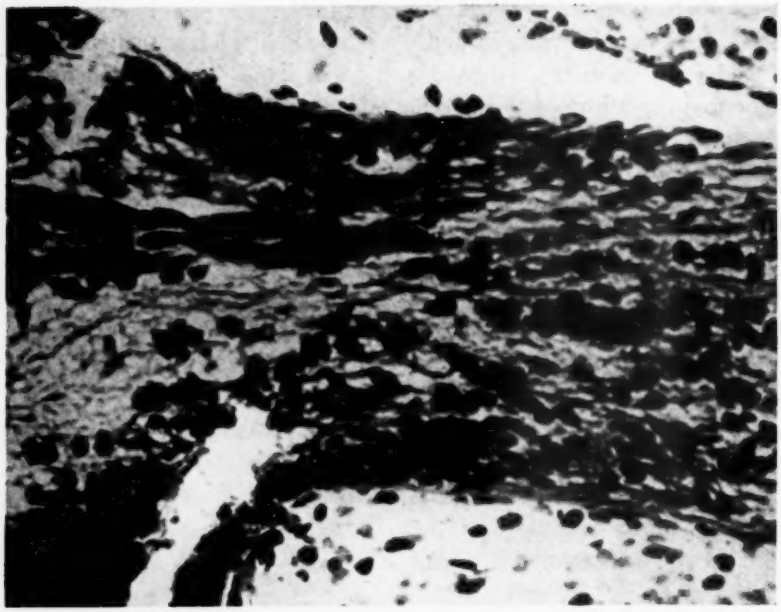

Fig. 2 (Haden). 20-mm. embryo, longitudinal section optic nerve.

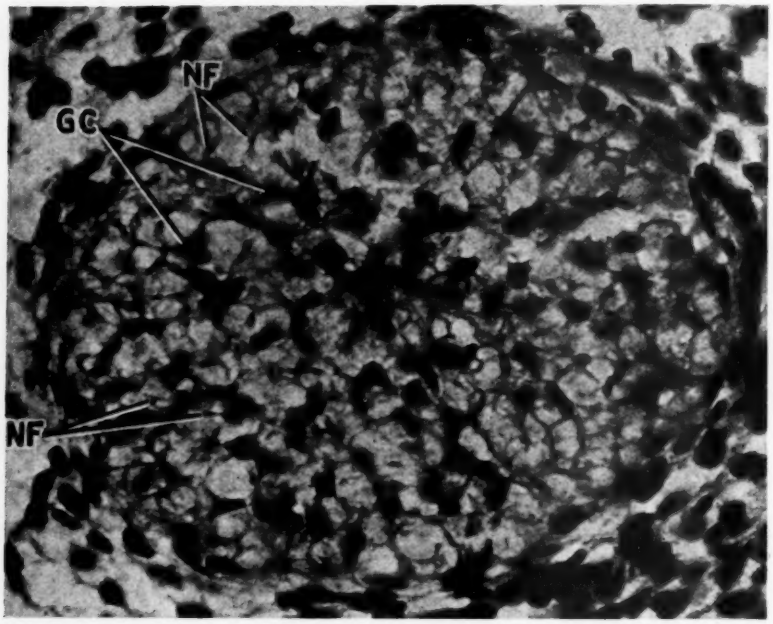

Fig. 3 (Haden). 20-mm. embryo, cross section of optic nerve. GC, glial cells with anastomosing processes; NF, nerve fibers.

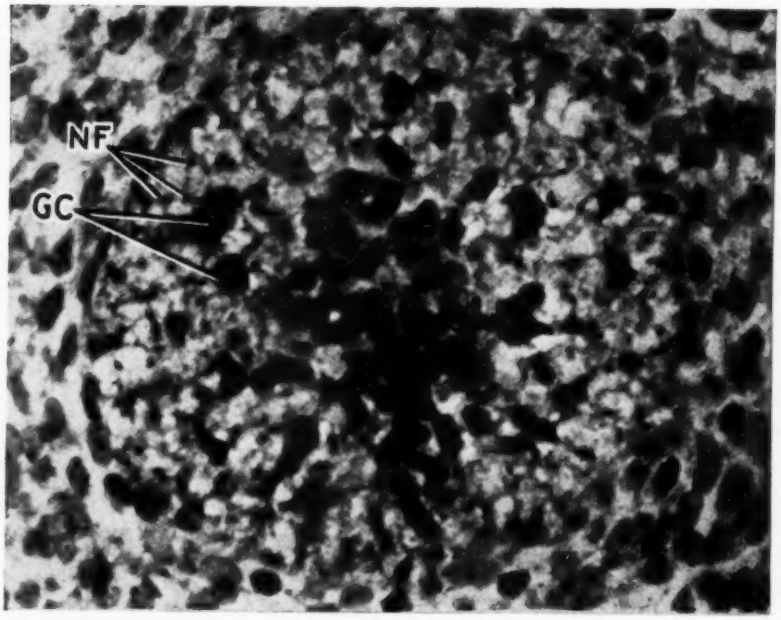

Fig. 4 (Haden). 20-mm. embryo, cross section of mid-orbital portion of optic nerve. GC, glial cells; NF, nerve fibers.

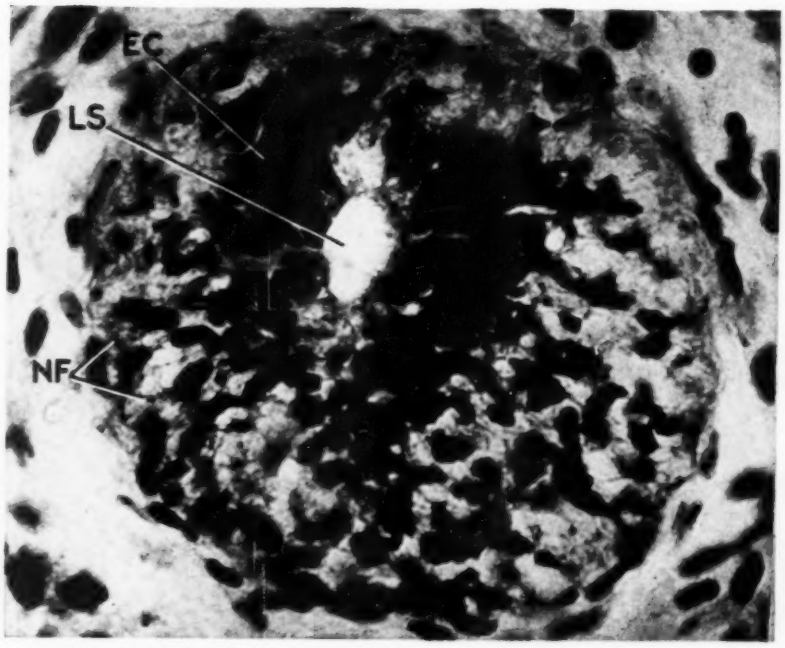

Fig. 5 (Haden). 20-mm. embryo, cross section optic nerve posterior third. LS, lumen of stalk; EC, epithelial cells; NF, nerve fibers.

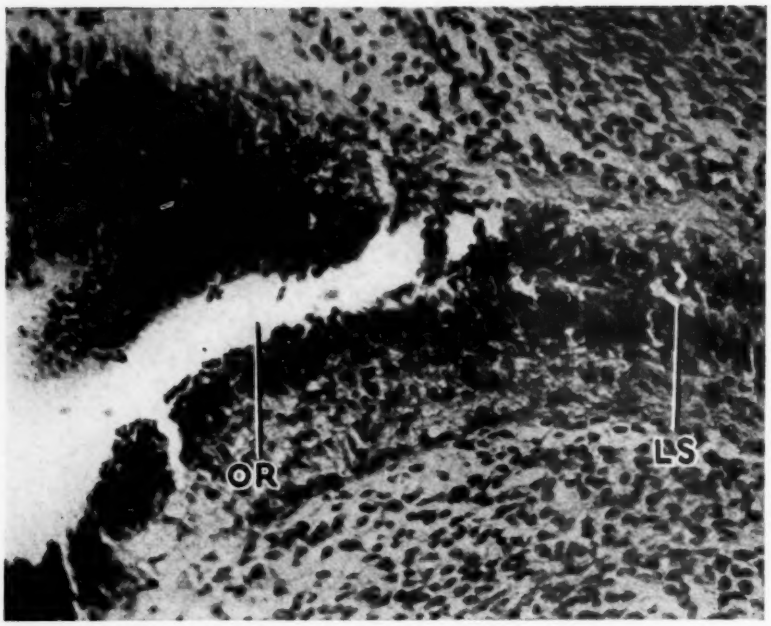

Fig. 6 (Haden). 20-mm. embryo, longitudinal section optic nerve posterior third. LS, lumen of stalk; OR, optic recess.

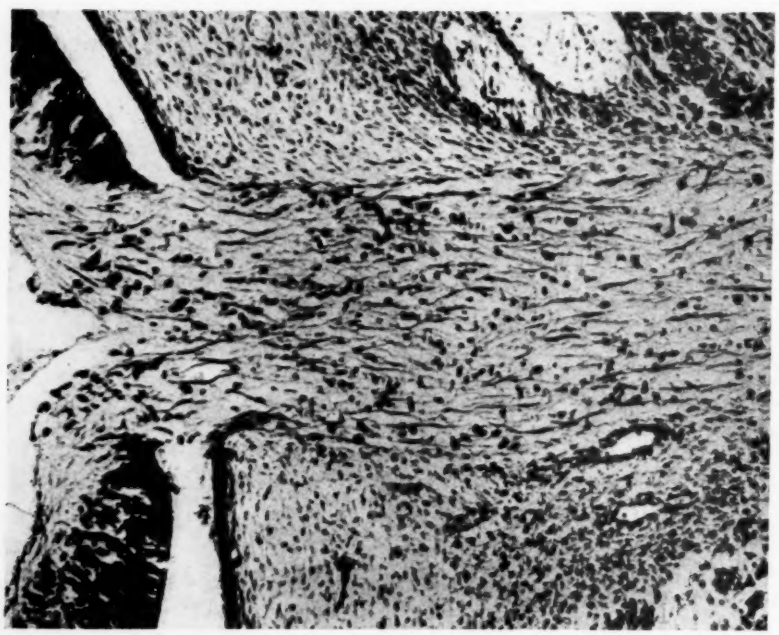

Fig. 7 (Haden). 29-mm. embryo, longitudinal section optic nerve.

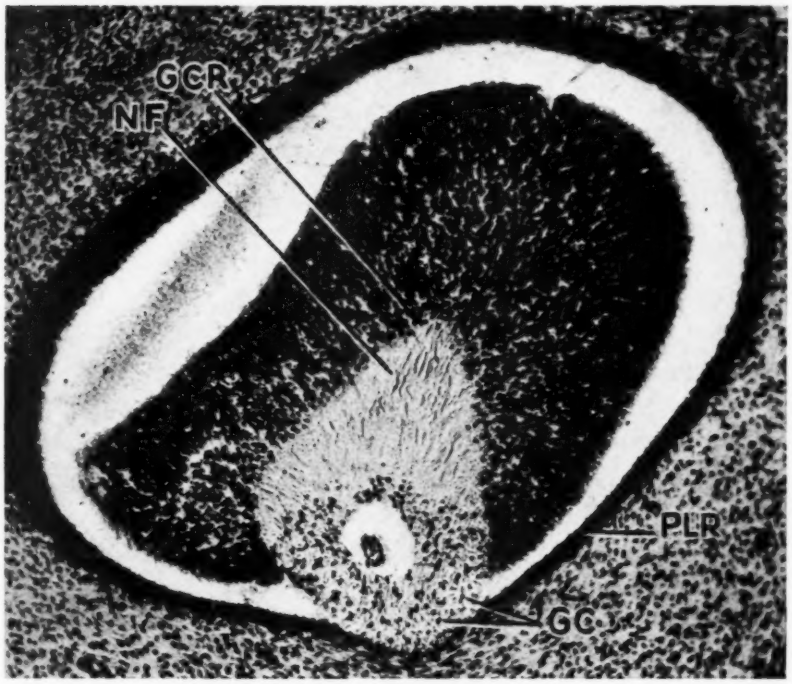

Fig. 8 (Haden). 29-mm. embryo, cross section optic nerve and oblique section of retina. GCR, ganglion cells retina; NF, nerve fibers; GC, glial cells; PLR, pigment layer retina.

Fig. 9 (Haden). 45-mm. embryo, longitudinal section optic nerve. BP, Bergmeister's Papilla; NF, nerve fibers; PGM, peripheral glial mantle; PLR, pigment layer retina.

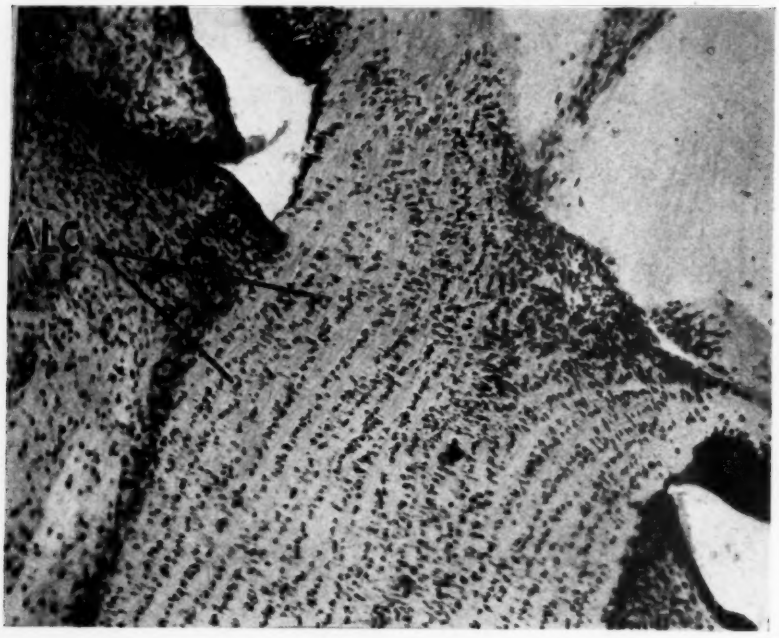

Fig. 10 (Haden). 67-mm. embryo, longitudinal section optic nerve. ALC, anlagen of laminae cribrosae.

Fig. 11 (Haden). 97-mm. fetus, longitudinal section optic nerve. S, septa, glial cells, and fibrous connective tissue.

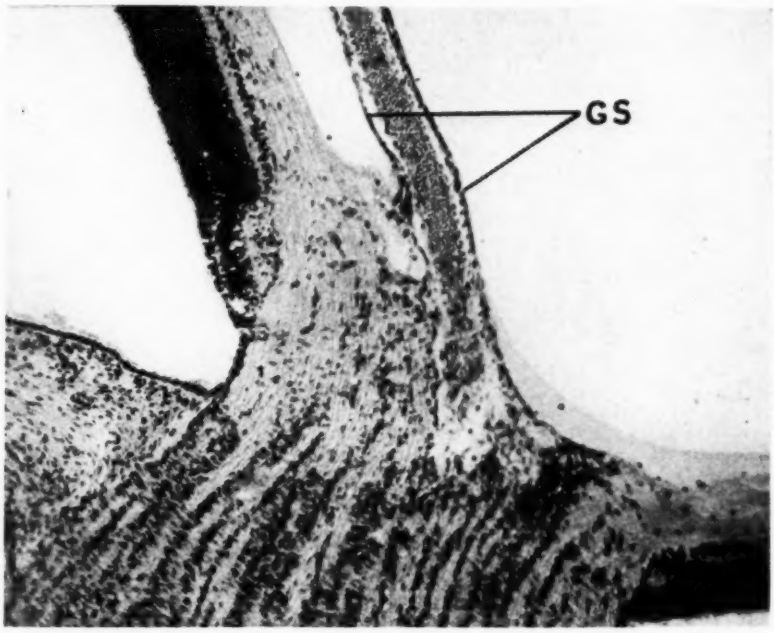

Fig. 12 (Haden). 160-mm. fetus, longitudinal section optic nerve. GS, glial sheath of hyaloid artery.

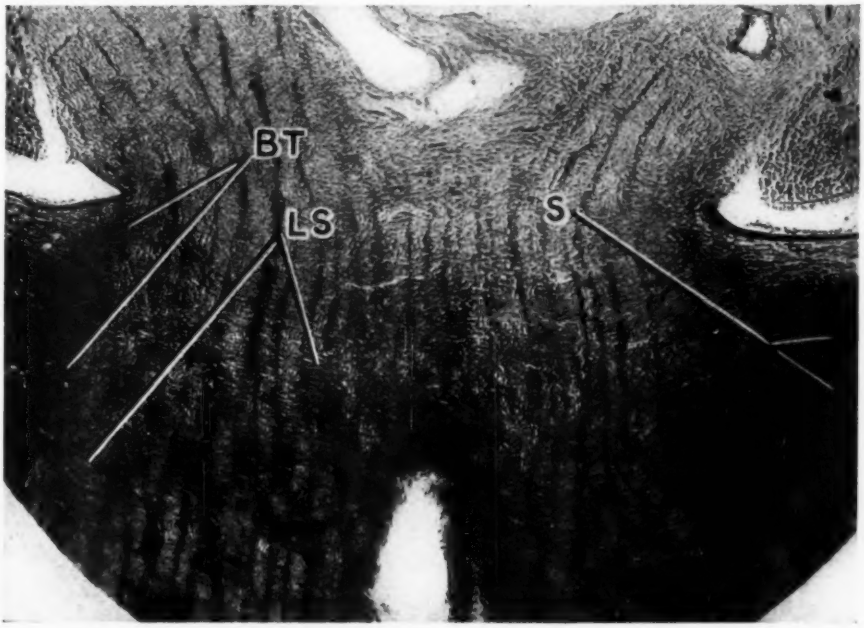

Fig. 13 (Haden). 500-mm. fetus, longitudinal section optic nerve. BT, border tissue; LS, lamina scleralis, connective-tissue lamina cribrosa; S, sclera.

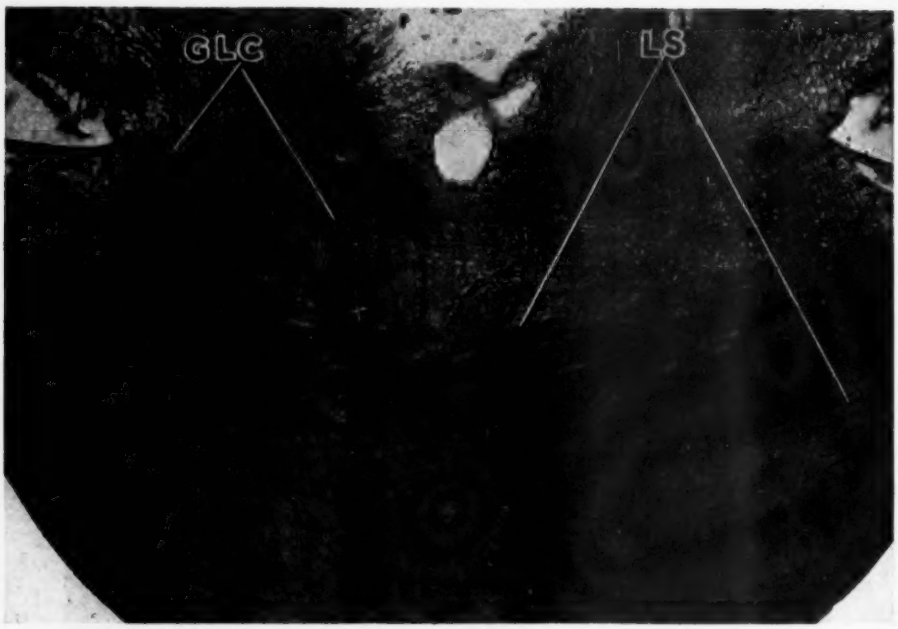

Fig. 14 (Haden). 2-months child, longitudinal section optic nerve. GLC, glial lamina cribrosa (lamina chorioidalis); LS, lamina scleralis (connective-tissue lamina cribrosa).

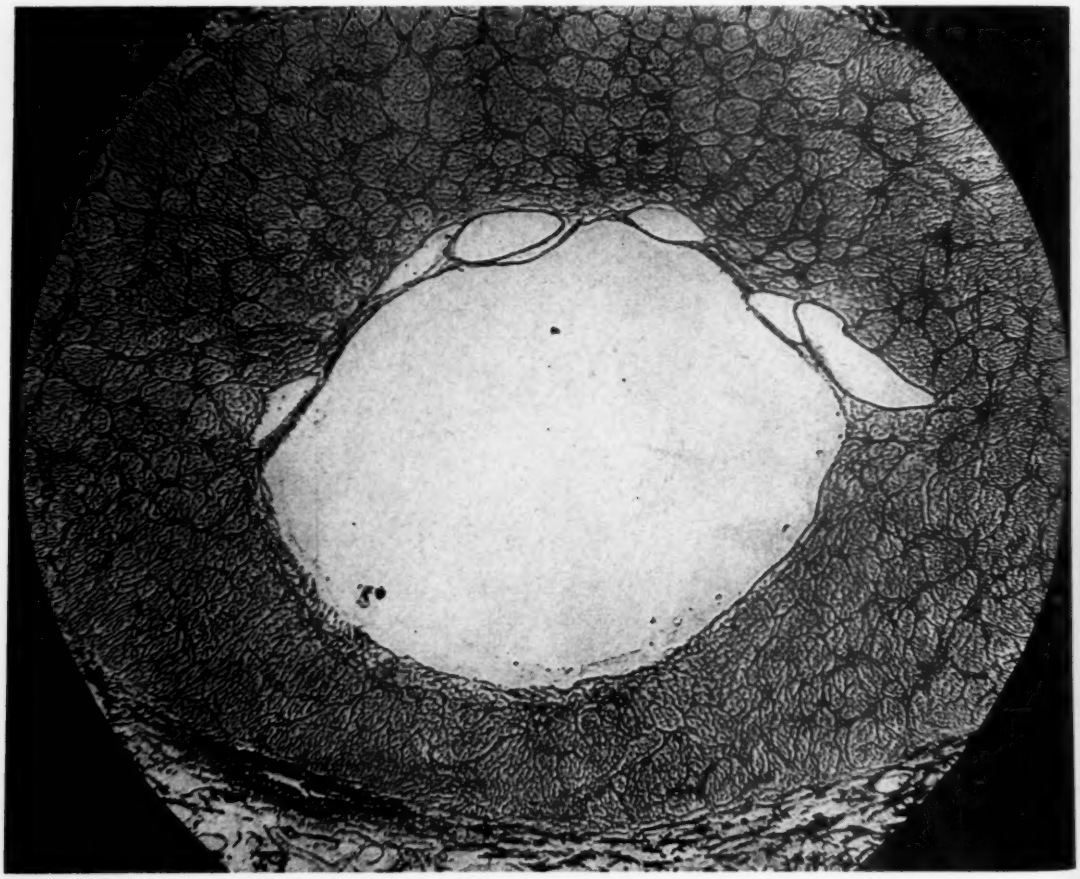

Fig. 15 (Haden). 2-months child, cross section optic nerve through glial lamina cribrosa, showing glial cells with anastomosing processes.

STREPTOMYCIN IN OPHTHALMOLOGY*

JOHN G. BELLOWS, M.D., AND CHESTER J. FARMER, PH.D.
Chicago, Illinois

Thousands of different strains and species of actinomyces, fungi, and bacteria have been investigated for antibiotic production and therapeutic usefulness; however, only penicillin and streptomycin, thus far, have proved to be of real therapeutic importance. Of the two, penicillin is far more valuable, yet streptomycin is superior to penicillin in the control of certain specific organisms. The therapeutic possibilities of streptomycin in ocular infections has aroused a great deal of interest. The literature is scanty and it must be emphasized that streptomycin therapy in ocular infections is still in the experimental stage.

Leopold and Nichols[1] have demonstrated that streptomycin administered to rabbits in dosages of 10,000 mcgm. per kg. body weight appears in the conjunctiva, sclera, extraocular muscles, and aqueous humor. Much larger doses (100,000 mcgm. per kg. body weight) are necessary for streptomycin to become detectable in the cornea, vitreous, chorioretinal tissues, and optic nerve. Streptomycin did not penetrate the intact cornea, but it readily penetrated the cornea if it was abraded or if iontophoresis was employed.

Owens[2] reported that an E. coli infection of the cornea responded satisfactorily to local treatment with this antibiotic. Alberstadt and Price[3] stated that streptomycin lessens the healing time of corneal infections. We[4] showed that intraocular injections of streptomycin, if administered in 6 to 8 hours, prevented experimentally produced vitreous infections. We found that streptomycin was unexcelled for the treatment of experimental and clinical B. pyocyaneus infections of the cornea. This antibiotic was also of value in some types of acute and chronic conjunctivitis. Molitor[5] reported that streptomycin even in the most purified form possesses neurotoxic properties. The large systemic doses required for the antibiotic to reach a detectable although not necessarily therapeutic level in the cornea, vitreous, chorioretinal tissues, and optic nerve might produce, during prolonged treatment, neurotoxic disturbances in man. If it were possible to achieve adequate therapeutic concentrations by local methods of administration, the toxic manifestations accompanying systemic administration would be avoided.

PURPOSE OF THIS REPORT

The purpose of this report is to describe the following investigations:

1. Factors which influence the penetrability of streptomycin through the cornea.
2. Local tissue tolerance following surface application and intraocular injection of streptomycin.
3. The effectiveness of streptomycin therapy in vaccinia keratitis with secondary infections.
4. Factors which influence the penetrability of streptomycin through the cornea.

EXPERIMENTAL PROCEDURE

We have confirmed the work of Leopold and Nichols in that streptomycin does not penetrate the normal cornea. In a series of normal rabbits anesthetized by intravenous injection of nembutal,

* From the Departments of Ophthalmology and Biochemistry, Northwestern University Medical School, Chicago, Illinois. This research was done under a contract between Navy Program for Basic Research and Northwestern University.

streptomycin hydrochloride, in concentrations of 5,000, 10,000, and 50,000 mcgm. per ml. of physiologic salt solution, was applied as a corneal bath by means of plastic eye cups for periods of 15 minutes to 4 hours. At the end of the designated period, the cup was removed, and the cornea and cul-de-sac were thoroughly washed with a stream of normal saline from a wash bottle. The aqueous was then withdrawn through a limbal puncture by means of a sterile 27-gauge needle attached to a tuberculin syringe. The streptomycin concentration of the aqueous was then determined by the method of Heilman[6] using B. megatherium. Values of less than 6.25 mcgm. streptomycin per ml. of aqueous could not be accurately determined by this method because of the small amount of aqueous (0.2 ml.) obtainable. They were, therefore, considered negative. Fluorescein staining at the end of the period established the absence of corneal damage. Out of the entire series of 24 rabbit eyes, only one showed a measurable amount. In this single animal a concentration of 50,000 mcgm. per ml. applied for three hours resulted in a concentration of 12 mcgm. per ml. aqueous.

Since the normal cornea prevents streptomycin from reaching the aqueous, attempts were made to increase the penetrability by the following means:

1. Corneal penetrability of streptomycin

a. Iontophoresis (ion-transfer). Leopold and Nichols showed that by means of iontophoresis, streptomycin could be made to penetrate the cornea in considerable amounts so that the concentrations in aqueous reached 30 to over 70 mcgm. per ml.

In preliminary electrophoretic experiments with solutions containing 100 mcgm. of streptomycin (HCl) per ml., assay of samples taken from the electrode chambers showed a concentration of less than 50 mcgm. at the anode and over 100 mcgm. at the cathode with currents of 0.8 to 0.9 milliamperes at 44 volts. In an extirpated rabbit eye, iontophoresis with a solution of 1,000 mcgm. streptomycin (HCl) per ml., using 22 volts and 2 milliamperes for 30 minutes with the anode connected to the solution cup and cathode inserted through the optic nerve into the vitreous, gave an aqueous concentration of 100 mcgm. per ml. In the living rabbit eye, iontophoresis of a solution containing 10,000 mcgm. per ml. for 30 minutes with a current of 2 milliamperes at 22 volts produced a concentration of 25 mcgm. streptomycin per ml. aqueous. These experiments clearly indicate that a therapeutic level of streptomycin may be achieved in the aqueous by means of iontophoresis.

b. Use of wetting agents. Bellows and Gutmann[7] employed wetting agents with sulfonamides and showed increased concentrations in the aqueous. It, therefore, seemed logical to follow these studies in an attempt to increase penetration for streptomycin to such an extent as to obtain effective therapeutic levels in the aqueous. Using the procedure already described, one drop of aerosol (O.T.) (0.5-percent solution) was added per ml. of streptomycin solution employing concentrations of 5,000, 10,000, and 50,000 mcgm. per ml. for periods of 30 minutes, 1 hour, and 2 hours. Assay of the aspirated aqueous revealed values of 25 to 50 mcgm. per ml. when a corneal bath with a concentration of 50,000 mcgm. streptomycin per ml. of solution was used for one hour. With 5,000 and 10,000 mcgm. streptomycin per ml., the values were below 6.25 units per ml. aqueous for periods of 30 and 60 minutes. In two cases, where 10,000 mcgm. were employed for a period of two hours, values of 25 mcgm. per ml. of aqueous were obtained.

In three eyes, where 10 drops of 0.5-

percent solution of aerosol (O.T.) were added to 1 ml. of solution containing 50,000 mcgm. of streptomycin (HCl), values of over 100 mcgm. streptomycin per ml. aqueous were obtained. However, this concentration of aerosol produced macroscopic corneal changes, as evidenced by staining of the cornea with fluorescein.

These studies indicate that corneal penetration to streptomycin may be safely achieved by the cautious use of relatively low concentrations of aerosol. Further work is in progress with other wetting agents.

c. The abraded or the inflamed cornea. Leopold and Nichols report values ranging between 14 and 21 mcgm. streptomycin per ml. aqueous 15 minutes after "drop installations" of a saline solution of streptomycin containing 50,000 mcgm. per ml. in rabbits with abraded corneas. In our experiments using the eye cup, solutions containing 10,000 mcgm. or more per ml. in saline for two hours gave values of over 100 mcgm. per ml. aqueous. Clinically streptomycin will be used on inflamed corneas. For this reason a study was undertaken to determine penetrability through the infected cornea. For this purpose 15 rabbit corneas were inoculated with vaccinia. When definite signs of corneal infection were manifest, the penetration studies were carried out using the eye cup with a 10,000 mcgm. streptomycin (HCl) per ml. of saline solution for 15-, 30-, and 60-minute periods. With the exception of two eyes, the values in the aqueous ranged from 25 to 200 mcgm. per ml. There was no apparent relation between the longer and shorter intervals of bathing and the assay values. This may possibly be explained on the basis of the size of the corneal lesions. Thus, it is noteworthy that in corneal infections local applications lead to therapeutic concentration of streptomycin in the aqueous humor.

2. LOCAL TISSUE TOLERANCE OF STREPTOMYCIN

a. Effect on regeneration of the corneal epithelium. As shown by Bellows,[8] the cornea is an excellent medium to ascertain information relative to the local tissue effect of drugs. Molitor noted that instillation in the rabbit eye of buffered solutions of streptomycin available at that time, containing "500 to 1,000 units per cubic centimeter," results in an immediate inflammatory reaction which disappears in 12 to 24 hours. Our experience with the present commercial streptomycin (HCl), as well as the highly purified streptomycin-calcium-chloride complex, shows that saline solution, containing 10,000 mcgm. per ml., upon instillation into the rabbit and human eye is well tolerated as evidenced by no greater degree of conjunctival redness than that occurring upon similar treatment with accepted ophthalmic solutions.* In a series of 30 clinical cases in which this concentration was employed for instillations into the eye, only one patient complained that the eyes seemed worse after use of the antibiotic. In no case was any injury to the cornea or conjunctiva noted.

In addition to the production of conjunctival redness and staining reaction of the cornea, another means of evaluating local toxicity of a drug is its influence upon the cornea following removal of epithelium by abrasion with sterile gauze. For these studies a series of rabbit corneas were abraded with gauze, and the completeness of denudation was established by staining with fluorescein. Of these animals, six received instillations of a saline solution of streptomycin (HCl) containing 10,000 mcgm. per ml. in the right eye, reserving the left as a control receiving saline simultaneously with the

* The samples of streptomycin used by us were kindly furnished by Dr. Robertson of Merck and Company, Inc., and show negative or minimal histaminelike effects.

treated eye. Two drops were instilled five times daily between the hours of 9 a.m. and 5 p.m. until the corneal epithelium had regenerated as evidenced by absence of staining with fluorescein. A second group of six rabbits was treated similarly with a streptomycin solution containing 50,000 mcgm. per ml., while a third group of six rabbits received 20 mg. of streptomycin powder at similar intervals.

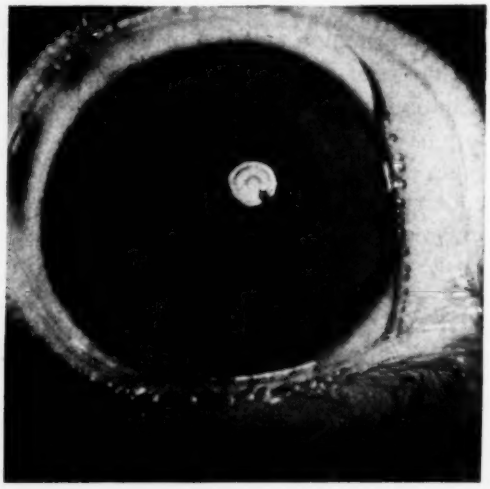

Fig. 1 (Bellows and Farmer). Abraded cornea receiving 10,000 mcgm. streptomycin per ml. saline.

In these experiments, corneas of the rabbits receiving instillations of the solution containing 10,000 mcgm. per ml. (fig. 1) healed at the same rate as those controlled with saline solution (3 to 5 days), thus showing no retardation in corneal regeneration due to the antibiotic solution. However, in rabbits receiving instillations of the 50,000-mcgm. concentration, there was a definite delay in healing to at least twice normal. The streptomycin powder delayed the regeneration of the epithelium even more markedly than the solution containing 50,000 mcgm. per ml. Furthermore, the cornea treated with either the 50,000-mcgm. concentration or with powdered streptomycin when finally healed showed marked vascularization and marked scar formation (fig. 2).

Since it is generally known that agents that are noninjurious to the cornea and conjunctiva of the rabbit are equally or even less irritating to that of the human eye, it may be concluded that streptomycin in concentrations of 10,000 mcgm. per ml. saline may be safely recommended for local application to the human eye. This has been proved subsequently by our clinical experiences with this antibiotic.

b. Effect of intraocular injection of streptomycin. As previously stated, even after huge systemic doses of streptomycin barely detectable amounts are found in the vitreous. It therefore follows that this method of administration would be ineffective except perhaps in infections with the most susceptible organisms. The present study was therefore undertaken to determine the tolerance of the ocular fluids and tissues to the direct injection of streptomycin. Also, to be determined was the length of time that an effective therapeutic concentration may be expected following a single intraocular injection.

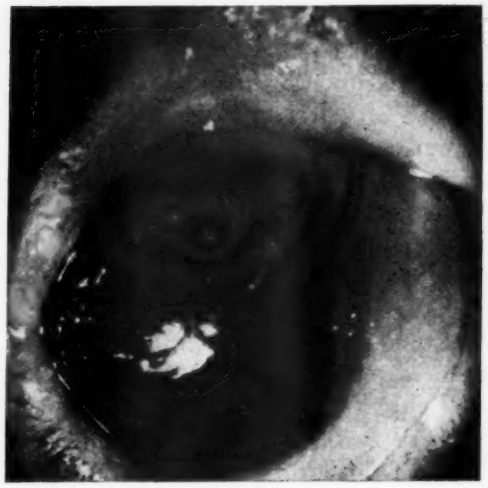

Fig. 2 (Bellows and Farmer). Abraded cornea receiving 50,000 mcgm. streptomycin per ml. saline.

For this study, solutions of various

commercial lots of streptomycin (HCl) and a highly purified sample of streptomycin-calcium-chloride complex, in concentrations ranging from 250 to 10,000 mcgm. per ml. were prepared in saline. The respective solutions in doses of 0.1 ml. were injected with a 27-gauge needle, making the puncture at the equator of the eyeball. Caution was practiced to deposit the streptomycin as near the center of the vitreous as possible. The eyes were observed daily with the ophthalmoscope, checking with the slitlamp to confirm ophthalmoscopic observations. At varying intervals, the eyes were removed for histologic study.

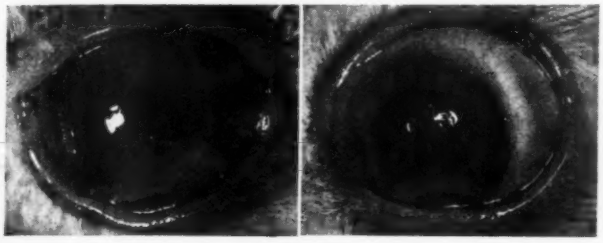

Fig. 3 (Bellows and Farmer). The picture at the left shows the vaccinia-keratitis infected control eye. At the right is the vaccinia-keratitis infected eye which has been treated with streptomycin.

For determining the retentive power of the vitreous for streptomycin, 100 mcgm. of the antibiotic in 0.1-ml. saline were injected into the vitreous in a series of rabbits. At specified intervals of 4, 8, and 24 hours the vitreous was removed and the streptomycin content determined.

The frequency and number of permanent vitreous opacities were low with the more purified commercial samples (21 eyes—6 opacities), and least with the highly purified streptomycin-calcium-chloride complex (19 eyes—4 opacities). In many instances the opacities were in the form of a "needle track" which gradually disappeared over a period of several weeks. An occasional posterior cortical or capsulo-cortical lens opacity appeared, which was attributable to trauma by the needle, or to the injection of the solution too close to the lens. In none of the animals where the fundus remained visible ophthalmoscopically was damage to the retina observed. Histologic sections of several eyes examined by Dr. Bertha A. Klien failed to reveal any changes in the tissues in those eyes receiving the injection.

The studies of streptomycin retention in the vitreous revealed between 12.5 to 25 mcgm. of streptomycin even 24 hours after its injection. Thus after a single intraocular injection of 100 mcgm. of streptomycin, an adequate therapeutic concentration may be expected for over 24 hours.

It may be concluded that the purer commercial forms of streptomycin may safely be injected into the vitreous. The initial changes observed are in many instances transient, and will probably be less marked in the human eye because of its size. These findings are similar to those obtained by von Sallmann[9] with penicillin. Therefore any theoretic objections to intra-vitreal injections of streptomycin in cases of infection of the vitreous with a sensitive organism are unfounded.

3. The effect of streptomycin on vaccinia keratitis

Our previous studies[4] had demonstrated the value of streptomycin in certain ocular infections. The following experiments were undertaken to determine the value of streptomycin in experimental vaccinia infections of the cornea in rabbits, and to study its effect on the accompanying secondary infection.

In a series of normal rabbits anesthetized by intravenous injections of nembutal, an area of each cornea was outlined with a 4-mm. trephine. The epithelium within this area was abraded by a knife, following which a drop of vaccinia was placed on the abraded region and the eye was kept open for 60 seconds. Previous experiments had shown that uniform infections of the cornea were obtained by this means. One hour after the inoculation, drops of streptomycin (10,000 mcgm. per ml. saline solution) were instilled into the right eye. These instillations were made three times daily until the end of the experiment. Before the inoculation and every morning at the same hour before daily treatments were started (about 16 hours after the last streptomycin had been applied the previous day) a single platinum loopful of material was taken from each conjunctival sac and inoculated on blood agar. Twenty-four hours later organisms were identified and colonies were counted. The two main organisms were Neisseria catarrhalis and Hemolytic staphylococcus albus. The results of the bacteriologic observations showed that up to the sixth day no differences in the number and type of organisms were noted.

However, after this period the number of colonies from the treated eye was consistently lower than in the control eye. As a result of the decreased amount of secondary infection in the treated eyes, the degree of scarring and vascularization in 80 percent of the corneas was much less marked than in the untreated eyes (fig. 3).

Summary

The penetrability of the cornea to streptomycin may be increased by abrasion, inflammation, ion-transfer, and wetting agents.

Streptomycin is safe and nonirritating to the surface of the eyeball in concentrations up to 10,000 mcgm. per ml. Higher concentrations delay the regeneration of the epithelium and promote scarring and vascularization of the cornea.

Intravitreal injections of 500 mcgm. of streptomycin in 0.1-ml. saline are well tolerated.

The vitreous retains an effective therapeutic concentration for over 24 hours following the intraocular injection of 100 mcgm. of streptomycin.

Local application of streptomycin decreases the amount of secondary infection accompanying vaccinia infections of the cornea. As a result of this, there is less scarring and vascularization of the corneas of the treated eyes.

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OPERATIVE TECHNIQUE OF VITREOUS REPLACEMENT*

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The purpose of this paper is to present in detail the simple and nontraumatizing technique of substituting a given amount of a patient's clear cerebrospinal fluid for an equal amount of cloudy vitreous. In developing the technique, which any well-trained ophthalmologist will find easier than standard operations for cataract or filtration operations for glaucoma, the simplest manipulation with the least complicated instruments was constantly sought after. The development of expensive and complicated apparatus was carefully avoided. Full advantage was taken of the published work of earlier investigators[1,2] on this problem, and of the cheerful generosity of the Research Department of Becton, Dickinson & Company, Inc., of Rutherford, New Jersey, who helped to develop and who supplied, gratis, the needles and syringes, which are the only special apparatus needed to perform this operation easily and successfully.

Using aseptic technique, a spinal tap is performed on the ward as short a time as possible before the operation. About 4 cc. of cerebrospinal fluid are collected in a dry, powder-free, cotton-stoppered, sterile test tube, which is carried directly to the operating room, where it is transferred into a sterile, dry, dust-free medicine glass on the instrument tray. Besides the ordinary instruments needed to perform an operation on the extraocular muscles, the following special items are required:

1 2-pronged corneal pick.

1 tube of 4-0 plain catgut on a cutting atraumatic needle.

1 tube of 4-0 black silk on a cutting atraumatic needle.

2 2½-cc. Luer-Lok syringes.†

2 Special 18-gauge needles with stylets.†

The pick is used to steady the globe when placing the purse-string suture of 4-0 plain catgut at the elected puncture site. The two special syringes are constructed with minimal clearance between plunger and syringe wall in order to avoid air leaks when suction on the vitreous is made, and the needles (fig. 1) have a stylet to prevent loss of vitreous when puncture of the sclera is made. One type of needle is cut off at right angles to the shaft so that no point exists to injure the retina or the lens when the eye collapses as vitreous is withdrawn. There is a stop, 12 mm. from the end of the needle, to prevent too deep penetration of the needle into the vitreous chamber at the time of puncture.

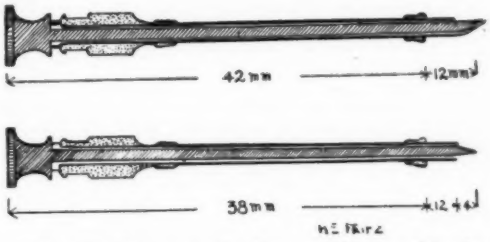

Fig. 1 (Fritz, *et al.*). Two needles used in the substitution of cerebrospinal fluid for cloudy vitreous.

Under pentothal sodium or local anesthesia, adrenalin (1:1,000) and pontocaine (0.5 percent) are applied to the eye topically. The eye speculum is inserted between the lids. A conjunctival incision is made parallel to and about 5 mm. from

* From the Eye-Bank for Sight Restoration, Inc. The expenses connected with this research were met by The Florence Ellsworth Wilson Memorial Fund Fellowship in Ophthalmology.

† Available upon special order from Becton, Dickinson & Company, Rutherford, New Jersey.

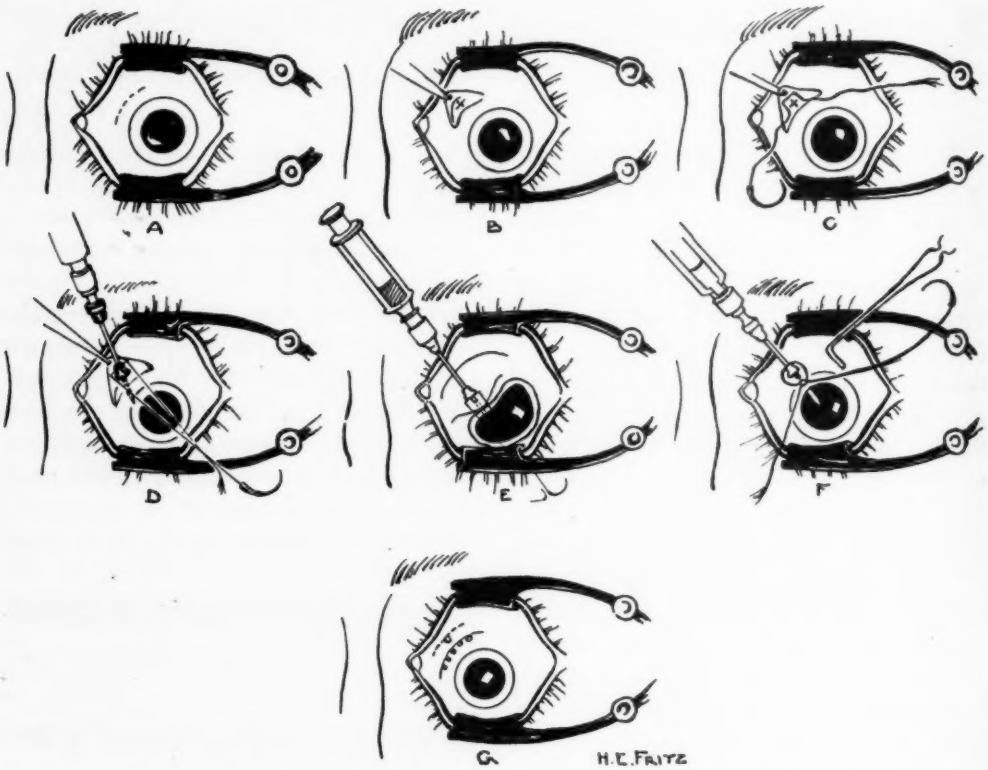

Fig. 2 (Fritz, *et al.*). The procedure is shown schematically as it is done on the left eye. A. With the eye speculum in place, the site of the conjunctival incision in the upper nasal quadrant is shown. B. The sclera is exposed and the conjunctiva has been retracted with a piece of 4-0 silk. The location of the puncture site is shown with a little cross. C. The three sides of the 1-mm. square of 4-0 plain catgut are shown placed in the sclera about the puncture site. D. The needle and stylet have been pushed through the sclera into the vitreous chamber as far as the stop. E. The stylet has been removed, the empty syringe has been inserted into the needle hub, and the cloudy vitreous has been drawn into the syringe. The eye is partially collapsed. F. The syringe with clear cerebrospinal fluid has been substituted for that containing cloudy vitreous. A quantity of cerebrospinal fluid roughly equal to that of the aspirated vitreous has been injected into the vitreous chamber. Some cerebrospinal fluid remains in the syringe. The needle tip can be seen through the pupil in the centrally cleared vitreous. Tension of the eye is just a trifle harder than it was preoperatively as estimated by touching the globe with a squint hook. G. The 4-0 plain-catgut suture has been drawn up and tied as syringe and needle were withdrawn. The conjunctival incision has been closed with a running stitch of 4-0 silk.

the limbus. It is of sufficient length to allow easy access to that portion of the upper nasal quadrant of the sclera which is 12 mm. from the limbus. The assistant draws 2½ cc. of the 4 cc. of cerebrospinal fluid previously obtained into one of the special syringes. While steadying the globe with the pick, three sides of a 1-mm. square of plain 4-0 catgut are placed at the chosen puncture site in the sclera (fig. 2). When the two ends are tied, a purse string will result by completing the fourth side of the square. The two ends of the suture are then used to steady the globe with one hand, while the special needle with stylet is pushed through the sclera up to the stop. The puncture site is, of course, the center of the square outlined by the catgut suture. The stylet is then withdrawn from the

needle and the empty 2½-cc. special syringe is inserted into the hub of the needle which has already been inserted up to its stop in the vitreous chamber. Gentle suction is then produced carefully, moving the syringe and needle in and out and from side to side until from 1¼- to 2¼-cc. of cloudy vitreous are withdrawn. All the vitreous that can be withdrawn without undue suction or trauma is taken and the amount varies, for reasons as yet unknown, between the quantities mentioned. As the globe collapses like a punctured basketball, the needle is not allowed to penetrate more deeply, and the position of the intravitreal end of the needle in relation to the lens and retina opposite is constantly kept in mind.

The syringe containing 2½ cc. of cerebrospinal fluid is now substituted for the one containing all the vitreous that could be aspirated. The fluid is then gently injected into the eye, which assumes its normal shape. With the index finger on the plunger, to prevent regurgitation of fluid into the syringe, the tension of the globe is determined with a squint hook, and it will usually be found that the amount of cerebrospinal fluid injected roughly equals that of the vitreous withdrawn. An extra drop or two of fluid may be injected without harm, the eye being left a little harder, if anything, than is judged to be normal. The assitant then makes a half hitch in the purse string, and draws it up snugly about the needle shaft, whereupon needle and syringe are withdrawn from the vitreous chamber. The assistant then completes the knot on the purse-string suture. Before withdrawing the needle, a glance through the dilated pupil can reveal the needle point in the vitreous chamber. The conjunctiva is then closed with the 4-0 silk suture. A 1-percent atropine-sulphate ointment is placed in the conjunctiva, and a single eye patch is applied. If the operator wishes to do so, an ophthalmoscopic examination may briefly be made and some idea of the ultimate result may be ascertained before ointment and dressing are applied.

Comment

In the development of this experiment, cerebrospinal fluid was considered ideal for several reasons. In the first place, it is easily available and doubtless has the same immunologic and other properties common to the body fluids of the individual patient. It is a substance more like vitreous than any other substance, with the exception of vitreous taken from a donor eye. Yet the properties of turgescence and deturgescence characteristic of a gel (and vitreous is considered to be one[3]) militate against the use of vitreous; whereas, cerebrospinal fluid being a sol does not change its volume. What happens to the mixture of cerebrospinal fluid and residual vitreous in the eye is as yet unknown.

Here at the Eye-Bank, the use of vitreous transplants (according to the method of Cutler[4]) from eyes enucleated elsewhere as donor eyes was considered. It has been found, however, that culture of the outside surface of such eyes[5] often yields bacterial growth. The effectiveness of the sclera and cornea as barriers against bacterial contamination of the vitreous is unknown. It is known that the vitreous of living human eyes is an excellent culture medium for bacteria, hence it was not considered justifiable to inject vitreous of doubtful sterility into the eyes, even though partially blind, of living human beings.

Refrigerated human eyes were used in the development of the needles and syringes. It was found that no more than 2¼ cc. of vitreous could be withdrawn, without undue suction or trauma, from enucleated normal eyes from 12 to 72 hours after enucleation at temperatures

from 34° to 72°F. No retinal detachment or ectopia lentis, which could with certainty be blamed on the aspiration of vitreous, was ever seen in these eyes. For these reasons, cauterization about the puncture site of living eyes and complicated pieces of apparatus, which would allow simultaneous injection and withdrawal of vitreous to maintain intraocular tension constant, were deemed superfluous.

The stop was placed on the shaft to prevent too deep penetration of the needle and stylet at the time of puncture. However, it must be remembered that this stop does not prevent the likelihood of scraping the lens or opposite retina as the eye collapses, unless this danger is kept constantly in mind. So far this has not happened in the refrigerated or living eyes. In fact, as withdrawal and injection are done, the eye should be suspended from the needle, rather than being allowed to sink into the eye as it collapses.

The stylet was used to supply a cutting point and to prevent loss of vitreous before the syringe could be placed in the needle, and the elimination of the needle point was thought to lessen the danger to ocular structures.

It is hoped that this detailed report will encourage ophthalmologists with suitable cases to perform this useful operation in order that its true place in the treatment of certain ocular conditions may be determined.

210 East 64th Street (21).

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BILATERAL GRANULOMATOUS UVEITIS FROM THE USE OF HORSE SERUM IN RABBITS*

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This report concerns a continuation of studies on the reaction of the rabbit eye to horse serum. In 1943, Davis and I found a close resemblance to the histopathologic picture of sympathetic ophthalmia in rabbit eyes injected with normal horse serum, but there was no evidence of uveitis in the opposite eyes.[1] By the use of another method,[2] consisting of an intraocular injection followed by one intravenously, a slight choroidal infiltration was found in 40 percent of the uninjected eyes. The purpose of the present investigation was to see if this contralateral uveitis could be increased.

This production of a uveitis in the uninjected eyes calls attention to the problems of sympathetic ophthalmia and of bilateral granulomatous uveitis. Sympathetic ophthalmia has never been produced in animals despite numerous attempts, but it has been roughly simulated by a number of investigators. In 1918, Woods, using an emulsion of homologous uvea injected into one eye, followed later by an intraperitoneal shocking dose, produced a sympathizing reaction in the contralateral eyes of dogs consisting of a round-cell infiltration of the anterior uvea but without epithelioid or giant cells.[3] In 1924, von Szily produced a bilateral intraocular inflammation with lymphocytes and epithelioid cells by inoculating the herpes virus into one eye only.[4] In 1924 and 1925, Guillery introduced capsules containing tubercle bacilli into the vitreous of one eye of rabbits and produced a bilateral uveitis resembling sympathetic ophthalmia.[5]

In 1929, Riehm concluded that horse serum absorbed from one eye produced an elective sensitivity in the fellow eye, resulting in uveitis after intravenous injections in pigmented rabbits but not in albinos.[6] He did not subject the pigmented and albino rabbits to identical procedures and apparently did not make a histologic study. By using a larger number of rabbits, identical procedures, and histologic study, I demonstrated, in 1944, an equal reaction in the eyes of pigmented and albino rabbits after an intraocular followed by an intravenous injection of normal horse serum.[2]

In 1929, Marchesani reported a contralateral reaction from repeated injections of avirulent organisms into one eye of rabbits. He first used *Bacillus subtilis*[7] and later *Bacillus xerosis* and *Staphylococcus albus*.[8] The lesion consisted of loose, nodular accumulations of mononuclear cells of various types. Marchesani concluded that the contralateral response was due to uveal allergy, but an allergic basis was disputed by von Szily[9] who showed that similar lesions could be produced by intravenous injections and by Iga who added that injections into an empty orbit would do the same.[10]

Friedenwald and Rones, in 1931, found essentially similar lesions in the human choroid as a result of septicemia and called this loose infiltration by mononuclear cells a "septic choroiditis."[11] Lucic, in 1939, used repeated intracutaneous injections of a combined culture of diphtheroids and a toxin-producing staphylococcus treated with tricresol to sensitize

* From the Research Division and the Department of Ophthalmology of the Indiana University Medical Center. Presented at the 16th scientific meeting of the Association for Research in Ophthalmology, Inc., at Atlantic City, June 10, 1947.

a group of rabbits. As a result of subsequent intraocular, intravenous, and intracarotid injections of *B. hoffmannii*, a contralateral response with epithelioid cells, giant cells, and pigment phagocytosis developed in the contralateral eyes.[12]

Preliminary investigation

In a search for the most favorable conditions for a contralateral response, a group of 38 rabbits was used to determine whether 1 or 2 weeks between intraocular and intravenous injections was the best interval and whether doses of 5, 10, 20, or 30 cc. of horse serum intravenously gave the best response.

Materials and Methods

Normal pigmented rabbits weighing from 4 to 7 pounds were examined with the aid of a flashlight, and those with diseased eyes were discarded. The right eyes were prepared with drops of 4-percent butyn and 1:1,000 merthiolate solution. The lids were opened manually by an assistant while a 25-gauge needle on a tuberculin syringe was used to make the intravitreous injection about 7 mm. behind the limbus in the 12-o'clock meridian. One-tenth of a cubic centimeter of sterile normal horse serum* preserved with 1:10,000 merthiolate was then injected. Most of this volume regurgitated leaving a subconjunctival bleb.

Both eyes were examined three times a week with flashlight and ophthalmoscope. After an interval of 1 or 2 weeks, an intravenous injection of either 5, 10, 20, or 30 cc. was given in the marginal ear vein. A week later the animals were killed by air embolism. The right eyes were subjected to six, and the left eyes to 12 scattered sections all stained with hematoxylin and eosin.

* Supplied by Eli Lilly and Company.

Results

Almost immediately after the intravenous injections, some of the rabbits went into anaphylactic convulsions and died. Many developed body sway, vestibular nystagmus, and head tilt. Weakness was common, with a few dying during the next two days. Of the 38 rabbits, 28 survived until the proper time for enucleation. Microscopic study of this latter group indicated that about 80 percent of the uninjected left eyes developed a mild mononuclear infiltration of the uvea typical of mild reactions observed in injected eyes. It was found that the 2-week interval between intraocular and intravenous injection, and the 20-cc. dose were best for the production of a contralateral uveitis.

Experiment 1

Right intraocular injection followed by repeated intravenous injections. The right eyes were injected as before. Repeated intravenous injections were used; the first was delayed for three weeks and subsequent ones were given at intervals of one week. Thirty-seven rabbits were divided into three groups to be enucleated one week after 2, 3, or 4 weekly intravenous injections of 20 cc. of sterile normal horse serum. The eyes were prepared, injected, examined, sectioned, and stained in the same manner as in the preliminary investigation.

Clinical observations

As a result of the repeated injections, only 12 of the 37 rabbits lived to the time for enucleation. In Figure 1 the reactions in the anterior ocular segment are plotted to demonstrate the average severity of the reaction on each day of the experiment. The reactions were graded from 0 to 4. Plus 1 indicates a slight conjunctival injection; plus 2, moderate bulbar conges-

tion and slight iritis; plus 3, conjunctival chemosis, pronounced bulbar congestion, and moderate iritis; plus 4, extreme chemosis and bulbar congestion, with strands of exudate over iris and pupil. Because the bulbar congestion almost disappeared during the later stages of the experiment, these criteria were varied for the later stages to include other signs such as a capsular clouding of the lens, haziness of the cornea, corneal vascularization, and keratectasia.

The clinical course can be described best by considering the periods between injections.

Features during the three weeks prior to intravenous injections

Right eyes. Following the injection into the right eyes, there was only a minimal reaction consisting of a slight circumcorneal hyperemia and a hazy vitreous in one fourth of the cases. At the end of five days this haze had increased until the visibility of the fundus was poor. The retinal vessels often were dilated. On the ninth day the reaction in the right eyes was pronounced and was rated at plus 2 or plus 3 in many of the rabbits. Fibrinous and cellular exudates were common on the irides and on the anterior lens capsules. Thereafter the fundi of the right eyes in most cases could not be visualized because of cloudy vitreous and anterior capsular opacities. When the fundi could be seen, vitreous veils were common, especially in the region of the retinal vessels. By the end of this 3-week period most of the bulbar congestion had disappeared, but some eyes with keratectasia were graded plus 3.

Left eyes. No reaction was observed for about two weeks. Then a mild dilatation of the retinal arteries and veins appeared.

Features during the week following the first intravenous injection

Right eyes. The reactions in the anterior ocular segment were again pronounced and more severe than before, usually plus 3 or plus 4.

Left eyes. Some of the left eyes began to present mild evidence of reaction, such

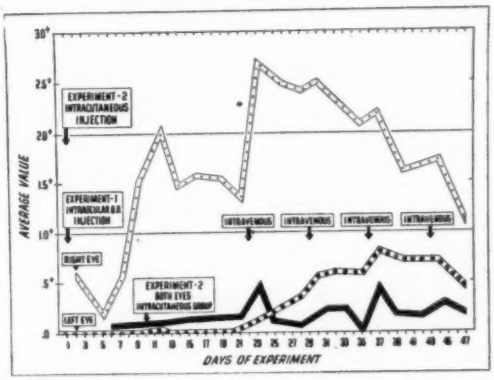

Fig. 1 (Schlaegel). The average intensity of reaction in the anterior ocular segment in right and left eyes of Experiment 1 and both eyes of Experiment 2 plotted against the time interval in days.

as slight circumcorneal injection and slight signs of iritis. In one case spots of cellular exudate were found on the anterior lens capsule. The severity of the reaction increased gradually during this week and a pronounced vitreous veil developed in one eye.

Features following second intravenous injection

Right eyes. There was a slight peaking of the response and then a gradual decline due to lessening of congestion.

Left eyes. The reaction remained roughly constant. There was nothing remarkable about the fundi until three days later when choroidal exudates developed along the retinal vessels and in the periphery along with haziness of the vitreous.

Features following third intravenous injection

Right eyes. Again there was only a slight congestive response with a subsequent decline of the degree of hyperemia. Two of the right eyes had generalized corneal relucence; one case developed occlusio pupillae, and another, corneal vascularization.

Left eyes. All left eyes were involved. In two thirds of them choroidal exudates were seen.

Features following fourth intravenous injection

Right eyes. The reaction was less than before with a continued abatement of congestion.

Left eyes. Engorgement and tortuosity of the veins and a haziness of the disc were prominent findings. The choroidal exudates were still visible.

Experiment 2

Intracutaneous injection followed by repeated intravenous injections. In an attempt to elucidate the mechanism of the contralateral ocular response of the first experiment a group of 16 rabbits were each given an intracutaneous injection instead of a right intraocular injection. One tenth of a cc. of sterile normal horse serum preserved with merthiolate was injected into the epidermis producing a distinct bleb. Otherwise these rabbits were treated as in the first experiment.

Clinical observations

In Figure 1, it can be seen that the average response in the anterior ocular segment shows a peaking in the intensity of the reaction after each intravenous injection, but that the general sweep of the reaction did not reach the intensity of the left or contralateral eyes in the first experiment.

After the first intravenous injection the retinal vessels appeared slightly dilated and tortuous. Choroidal exudates along the retinal vessels and in the periphery, haziness of the media, and haziness and hyperemia of the disc appeared during the following days. In general, the fundus picture was very similar to that in the uninjected eyes of the main experiment except that it was not as frequently seen nor as pronounced in development.

Figure 1 demonstrates that a pronounced reaction was present in the injected right eyes nine days after the intraocular injection of horse serum. Appreciable reactions appeared in the left or contralateral eyes around nine days after the intravenous injections were begun, while the curve of the intracutaneous group shows only slight peaking after each one. Figure 1 also indicates, especially in the injected eyes, a decline in the intensity of the reactions in the anterior ocular segment after the later intravenous injections. This phenomenon may be due to desensitization as a result of the large doses of serum.[13]

In Table 1, the clinical features of the three groups are summarized.

In addition to 12 scattered sections of both right and left eyes of the intracutaneous group, sections of muscle, liver, kidney, lymph nodes, spleen, lung, heart, and small and large intestine were obtained to see whether the horse serum produced a generalized response. A minimal reaction was found only in the myocardium and kidney, consisting of small accumulations of mononuclear cells. This minimal infiltration is of little significance because it may have been caused by other factors.

Ocular histopathology

In all three groups the choroid is the tissue most involved. There is only slight infiltration of the anterior uvea.

Injected eyes. Eye sections of rabbits

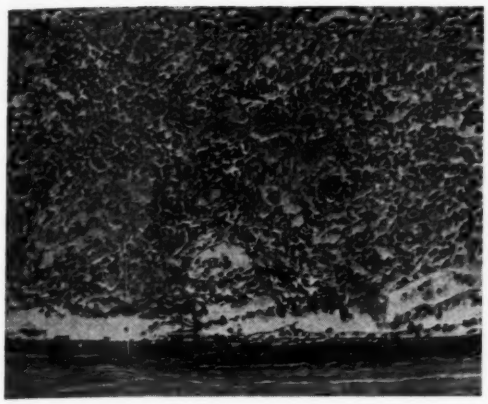

Fig. 2 (Schlaegel). Injected eye of a rabbit which died immediately after the second intravenous injection. The choroid has been increased to 20 times its normal thickness. There is an extension of the infiltration into the inner lamellae of the sclera.

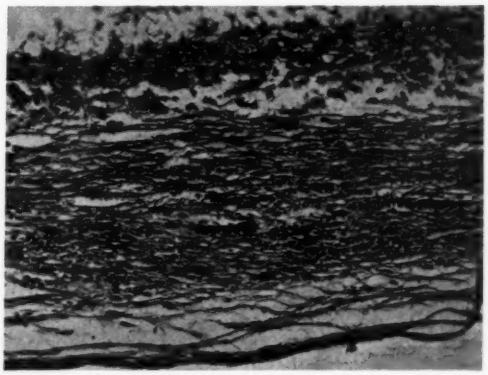

Fig. 3 (Schlaegel). Injected eye of a rabbit which received three intravenous injections. This case shows the most striking absorption of the infiltrate and its replacement by fibrous tissue. The choroid and retina have been converted into fibrous membranes.

which died early show the choroid of injected eyes to be heavily infiltrated with pale areas of epithelioid and occasional giant cells in no definite arrangement, lying in a darker field of lymphocytes, plasma cells, and large mononuclears (fig. 2). After 5 to 7 weeks the cellular infiltration is being replaced by fibrous tissue (fig. 3). This fibrosis involves both the retina and choroid. In one eye in which there was a tremendous thickening of the

TABLE 1

CLINICAL FEATURES IN RIGHT AND LEFT EYES OF 37 RABBITS OF EXPERIMENT 1 (FIRST INJECTIONS IN RIGHT EYES) AND IN BOTH EYES OF 16 RABBITS OF EXPERIMENT 2 (FIRST INJECTIONS IN SKIN)

Objective Signs	Experiment 1		Experiment 2
	Right Eyes (injected)	Left Eyes (uninjected)	Both Eyes (uninjected)
Early			
Circumcorneal injection	+	+	+
Fibrin in anterior chamber	+	0	0
Vitreous haze	+	+	+
Blurring of iris pattern	+	+	0
Anterior Segment			
Haziness of cornea	+	+	0
Corneal vascularization	+	0	0
Keratectasia	+	0	0
Posterior synechiae	+	0	0
Occlusio pupillae	+	0	0
Iris bombé	+	0	0
Capsular clouding of lens	+	+	0
Fundus			
Veils in vitreous	+	+	0
Congestion of retinal vessels	+	+	+
Hyperemia and blurring of disc	+	+	+
Chloroidal exudates	+	+	+
Pronounced vitreous haze	+	0	0

Fig. 4 (Schlaegel). Cellular infiltration of extraocular tissues.

former retina by heavy fibrous tissue, the use of special stains, including phosphotungstic acid hematoxylin, demonstrated an absence of gliosis.

One of the severely reacting injected eyes will be described. It was the only case sectioned that showed appreciable corneal changes.

Description of one injected eye

Mononuclears, especially plasma cells, are found between the lamellae of the anterior two thirds of the cornea. Capillary loops extend to near the center of the cornea in the infiltrated region. A heavy collection of mononuclear cells is found superficially at the limbus. In its posterior portion, the iris is mildly infiltrated mainly with plasma cells. A heavy fibrous cyclitic membrane stretches out from the

TABLE 2

HISTOPATHOLOGIC FEATURES IN RIGHT AND LEFT EYES OF 12 RABBITS OF EXPERIMENT 1 (FIRST INJECTIONS IN RIGHT EYES) AND IN BOTH EYES OF 7 RABBITS OF EXPERIMENT 2 (FIRST INJECTIONS IN SKIN)

Histopathologic Features	Experiment 1		Experiment 2
	Right Eyes (injected)	Left Eyes (uninjected)	Both Eyes (uninjected)
General Features			
Infiltration almost entirely in uvea	+	+	+
Thickening due to: lymphocytes	+	+	+
large mononuclear phagocytes	+	+	+
plasma cells	+	+	rare
epithelioid cells	+	+	rare
giant cells	+	0	0
Dark areas of various mononuclear cells	+	+	0
Pale areas of epithelioid cells	+	+	0
Slight pigment phagocytosis	+	0	0
Iris infiltrated in posterior layers	+	+	0
Choroid			
Main site of cellular infiltration	+	+	+
Thickened to 5 times normal width	+	+	0
Late absorption of infiltrate with fibrosis	+	—	—
Sclera			
Cells infiltrate the inner lamellae	+	+	0
Mantle formed around perforating vessels	+	+	0
Pigment Epithelium			
General disintegration	+	0	0
Nodules resembling Dalen-Fuch's type	+	0	0
Orbit			
Infiltration of subconjunctival tissues	+	+	0
Infiltration of orbital tissues	+	+	0
Retina			
Late disorganization and fibrosis	+	—	—
Mild infiltration after necrosis	+	—	—

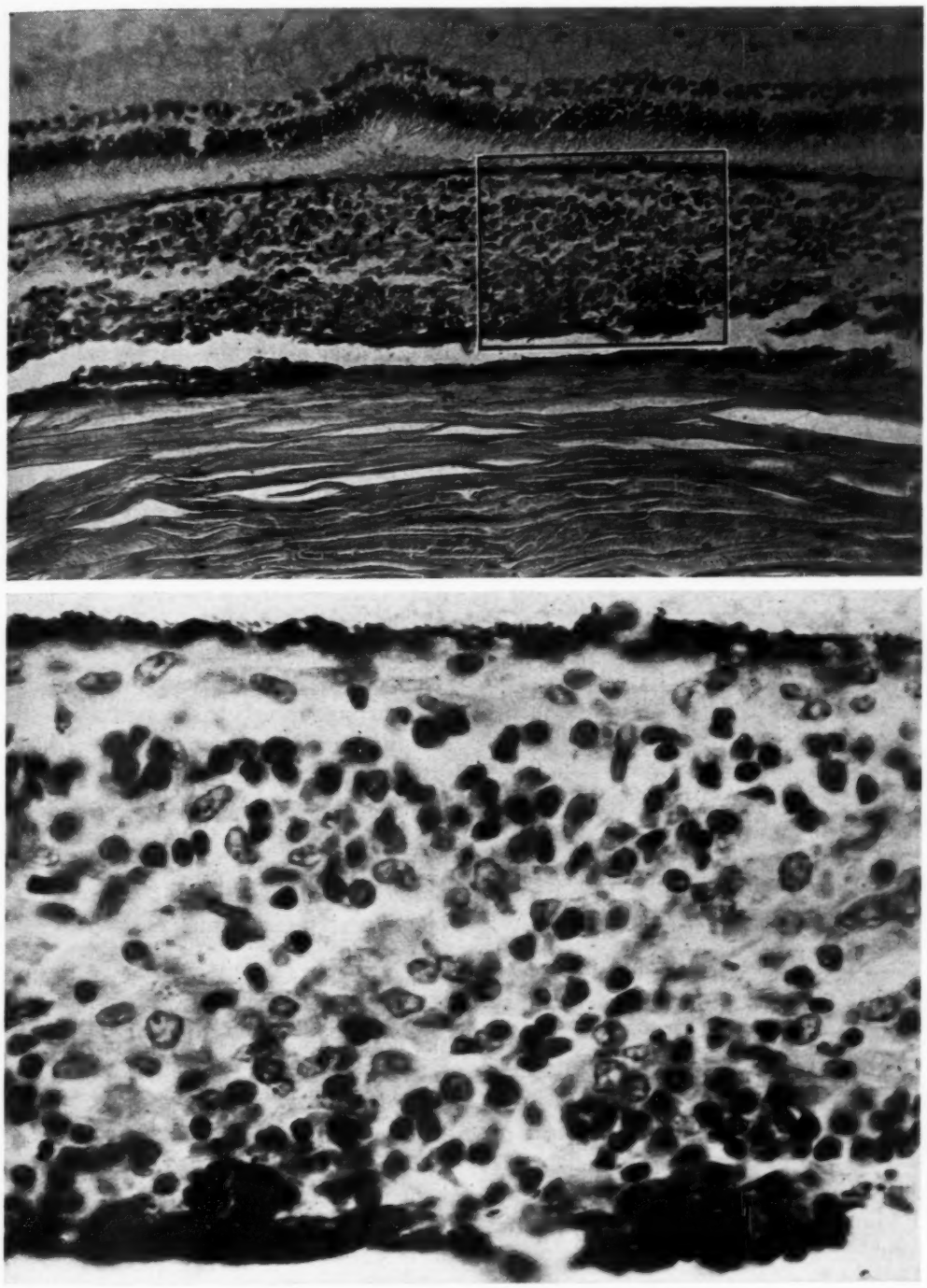

Fig. 5 (Schlaegel). Contralateral eye. *Above:* The choroid has been bulged up to five times its normal thickness by an infiltration with lymphocytes, large mononuclear phagocytes, plasma cells, and by areas of epithelioid cells. *Below:* High power of area outlined above.

ciliary body and extends behind the lens. The retina and choroid have been converted into one common membrane. The retina is necrotic and no longer recognizable. It is mildly infiltrated by extension from the choroid. The choroidal infiltration, consisting mainly of plasma cells has become somewhat thinned out and the fibrous tissue more abundant. The cells from the choroid have extended into the inner lamellae of the sclera and they form a mantle around the perforating vessels. The orbital tissues are involved by the same type of cells (fig. 4). At the optic disc the nerve and its septa are mildly involved and there is an extension of the choroidal infiltration back along the leptomeninges.

TABLE 3

SEVERITY OF UVEITIS UPON MICROSCOPIC EXAMINATION OF RIGHT AND LEFT EYES OF EXPERIMENT 1 (FIRST INJECTIONS IN RIGHT EYES) AND IN BOTH EYES OF EXPERIMENT 2 (FIRST INJECTIONS IN SKIN), GROUPED ACCORDING TO TIME OF ENUCLEATION

	Experiment 1 Right Eyes (injected)	Experiment 1 Left Eyes (uninjected)	Experiment 2 Both Eyes (uninjected)
After Second Intravenous:			
	3.0	2.0	1.0
	4.0	2.0	1.5
	2.0	1.5	0.5
	3.0	3.0	1.0
Mean	3.0	2.12	1.0
After Third Intravenous:			
	4.0	1.5	1.0
	3.0	1.5	1.0
	3.0	1.5	1.0
	3.0	1.0	0.5
Mean	3.25	1.37	.87
After Fourth Intravenous:			
	3.0	1.5	1.0
	4.0	2.5	1.5
	2.5	1.0	1.0
	4.0	2.5	1.0
	—	—	0.5
	—	—	0.5
Mean	3.37	1.87	.9
Mean of 3 groups	3.2	1.8	.9

Contralateral eyes. In the uninjected left eyes of Experiment 1, microscopic study reveals cellular infiltration in every case. Although the degree of cellular infiltration is greater than in a previous experiment[2] and in the preliminary test of this investigation, it is not as severe as in the injected eyes (table 3). This contralateral infiltration consists of large mononuclears, lymphocytes, plasma cells, and epithelioid cells bulging the choroid up to five times its normal thickness (fig. 5). No giant cells or large epithelioid cell aggregates were produced.

Description of one contralateral eye

There is a mild mononuclear infiltration in the superficial tissues at the limbus. There is only a minimal infiltration of the posterior half of the iris, the choroid being the tissue most involved. This choroidal infiltration is diffuse with nodular bulgings. It has caused a mild infiltration of the inner lamellae of the sclera, and a mantle around the perforating vessels. There are a few collections of cells in the orbital tissues. The ciliary body is mildly involved in its inner and posterior portions. The cornea, retina, pigment epithelium, and optic nerve remain uninvolved.

Three main features serve to differentiate the injected response from that in the contralateral eyes: (1) Heavier cellular infiltration. (2) Distortion, necrosis, and infiltration of the retina. (3) Replacement fibrosis.

Eyes of the group sensitized by intracutaneous injection. In some of the eyes the choroidal infiltration is so slight that it is difficult to tell whether wandering cells are present. The choroid is the only tissue involved. There is only a minimal diffuse infiltration of lymphocytes and large mononuclear phagocytes. Plasma

cells and epithelioid cells are seldom seen. The impression gained is that of a mild replica of the reaction in the other two groups.

In Table 2, the histopathologic features of the three groups are outlined. In Table 3 is shown the degree of histopathologic response in each eye sectioned. This table clearly demonstrates a severe reaction in the injected eyes, a moderate response in the contralateral eyes, and a minimal reaction in the eyes of the intracutaneous group. It also shows that there is no significant difference between the reactions when 2, 3, or 4 intravenous injections were used. Replacement fibrosis in injected eyes, however, was more common and prominent after the longer intervals. The criteria for the grading of the histopathologic response are as follows: Plus 1, minimal uveal infiltration by lymphocytes and large mononuclears; plus 2, the infiltration including plasma and epithelioid cells fills the whole thickness of the choroid; plus 3, moderate distension of the choroid by the infiltration; plus 4, pronounced distension of the choroid by an infiltration which includes giant cells.

Controls

Two minor controls were negative.

1. Twenty normal rabbit eyes were sectioned to determine the amount and type of cells normally found in the rabbit uvea. Each eye was subjected to six scattered sections stained with hematoxylin and eosin. The thinness and compact structure of the choroid was a striking feature. There was no evidence of wandering cells in the choroid of any of these eyes, but in the irides, plasma cells were common in the posterior one third of a few sections.

A study of these normal control eyes confirmed the reality of the cellular infiltration in the uninjected eyes of Experiments 1 and 2.

2. To check on the possibility that the merthiolate preservative in the horse serum played a role in the histopathologic response, a group of seven rabbits were each given a right intraocular injection of 0.1 cc. of 1:10,000 solution of merthiolate. (This solution was made roughly isotonic by mixing one part of a 1:1,000 solution of merthiolate with nine parts of sterile normal saline.) The right eye of one of these rabbits was enucleated each week and subjected to three scattered sections. Upon microscopic study no lesions were noticed, so it may be concluded that the merthiolate played no direct role in the production of the histopathologic picture.

Comment

1. Localization of the cellular reaction in the uvea

A striking characteristic of the reaction of the rabbit eye to horse serum is the localization of the cellular infiltration in the uveal tract. In the injected eyes there is no infiltration into the retina until it has become completely disorganized and the membrane of Bruch largely destroyed. In the uninjected eyes the retinas are unaffected and involvement of the sclera appears to be due to direct extension from the choroid. One might expect the uvea to be the site of predilection after intravenous horse serum because of its rich vascular character, but the uvea is also the site of predilection after a single injection into the vitreous. This uveal reaction is not explained by the studies of Thompson, Gallardo, and Khorazo who found no precipitins in the retina and choroid following intravenous egg albumin.[14] The greatest precipitin concentration was found in the corneal-tissue juice. Although several injected eyes of the present experiment developed vascularization of the cornea, such a reaction was unusual while the uvea was involved in every case.

This predilection of cellular infiltration for the uveal tract is not confined to the effects of horse serum. It has been demonstrated over a period of many years by numerous investigators using various substances. Marchesani, for example, described, after repeated injections of avirulent organisms into one eye, a reaction in the choroid of the contralateral eyes that apparently would be hard to differentiate from the effects of horse serum.[7, 8] This similarly brings up the possibility of contamination of the horse serum used in my experiments. However, it was received in a sterile condition preserved with merthiolate. It was handled with aseptic technique, and aerobic and anaerobic cultures of samples during the course of the experiment failed to grow any organism. If any surgical contamination occurred, it was in all likelihood so slight that the rabbits' natural defenses were protective. This supposition is supported by the fact that in no instance has a rabbit eye injected with horse serum ever demonstrated any sign of purulent inflammation.

TABLE 4

STATISTICAL COMPARISON OF THE CLINICAL REACTIONS IN THE ANTERIOR OCULAR SEGMENT OF THE UNINJECTED EYES OF EXPERIMENT 1 (FIRST INJECTIONS IN RIGHT EYES) AND OF EXPERIMENT 2 (FIRST INJECTIONS IN SKIN) ON THE DAYS FOLLOWING THE LAST THREE INTRAVENOUS INJECTIONS

	Exp. 1 (Left Eyes)	Exp. 2 (Both Eyes)	Exp. 1 (Left Eyes)	Exp. 2 (Both Eyes)	Exp. 1 (Left Eyes)	Exp. 2 (Both Eyes)
Day of Experiment	30		37		44	
Number of Eyes	15	16	10	10	4	6
Average Reaction	.57	.28	.85	.55	.75	.33
Standard Deviation	.073	.026	.023	.037	.028	.026

2. CHARACTER OF THE CELLULAR REACTION

The qualitative and quantitative differences in the cellular infiltration among the three groups (injected, contralateral, and intracutaneous) seem to depend entirely upon the differences in the severity and duration of the response.

A. Correlation of duration of reaction with types of cells. In 1943 we demonstrated that 12 hours after the eye of a previously sensitized rabbit is injected with horse serum the cellular infiltration is composed solely of polymorphonuclear leukocytes. After 24 hours, mononuclear cells predominate and soon entirely replace the polymorphonuclears.[1] With the passage of more time and following a severe reaction, large numbers of epithelioid cells and a few giant cells appear.

In some granulomatous diseases, especially tuberculosis, a similar sequence takes place, the dominant cell varying with the age of the lesion. Early there are polymorphonuclear leukocytes; later the mononuclear cell and lymphocyte are dominant; and still later giant cells and epithelioid cells are common.

B. The possible role of lipids. Sabin, Doan, and Forkner have shown that lipids from tubercle bacilli act as maturation factors for monocytes or large mononuclear phagocytes, converting them into epithelioid cells and epithelioid cells into

Langhans giant cells.[15] Also, lipid extracts from pyogenic bacteria, such as the colon bacillus, will give rise to epithelioid and giant cells.[16] In the case of horse serum the granulomatous response may be due to the lipid degradation products of horse serum broken down by an antigen-antibody reaction or by tissue lipases. Or it is possible that the response may be due to lipids set free from the uveal tissues themselves.

The presence of lipids in bacteria and in body tissues may explain why similar granulomatous responses have been obtained from a variety of different agents.

3. Is the contralateral response related to an increased quantity of horse serum entering that eye?

The eyes contralateral to those injected developed a significantly greater clinical and microscopic reaction than the eyes of rabbits sensitized by intracutaneous injection. The histopathologic reaction was twice as great. This difference is obvious upon examination of the microscopic slides and was found to be statistically reliable in computation of the probable error of the gradings.

The clinical reaction was also roughly twice as great in the contralateral eyes. In Table 4 the figures for the peak reactions following the last three intravenous injections are given. It can be seen that the average reactions on these specified days are statistically different as far as can be determined in a clinical investigation of this sort.

These results may be explained partially by the work of Guy who found that the following procedures would facilitate the passage of horse serum into the anterior chambers of both eyes: (1) An injection of horse serum into the anterior chamber of one eye. (2) Repeated intravenous injections. (3) Large intravenous injections.[17]

In the present experiments, including the preliminary tests, a greater reaction was obtained: (1) When one eye instead of the skin was injected. (2) When two or more intravenous injections were used. (3) When the intravenous doses were large.

These findings parallel and confirm those of Guy. Since he found that such procedures increased the penetration of horse serum into the contralateral eyes, it may be that a greater penetration was the cause of the more pronounced reaction in the uninjected eyes of Experiment 1 as compared to those of Experiment 2. The reasons for this assumed greater penetration were not learned, but there are at least two possibilities which should be considered.

1. A dilatation of the retinal arteries and veins was observed in the contralateral eyes two weeks after the intraocular injection. A similar vasodilatation in the uveal tract might result in an increased transudation of horse serum from the blood stream. In the group sensitized by the intracutaneous route such a retinal vasodilatation was not found prior to the intravenous injections.

2. A second possibility is that the eye is superior to the skin as a site for general sensitization of the rabbit. In a rabbit with a greater degree of general sensitivity, it is possible that transudation of horse serum into an uninjected eye might be increased or that once present its ability to incite a response is enhanced. However, this supposition of greater general sensitivity is not very well substantiated by a comparison of the number of rabbits dying of anaphylaxis in each group. In the first experiment 68 percent, and in the second, 57 percent, died as a result of the intravenous serum. This difference is hardly significant, indicating that roughly the same degree of sensitivity developed in both groups.

4. Comparison with some clinical types of granulomatous uveitis

The clinical reactions in the anterior ocular segment were not typically granulomatous in type due mainly to minimal iris involvement and to the presence of an anaphylactic congestive phase. The histologic reaction was more obviously of a granulomatous character and it is this histologic picture which will be compared to some of the clinical types of granulomatous uveitis.

A. Sympathetic ophthalmia. The histopathologic features of the reaction of the rabbit eye to normal horse serum, as compared to the features of sympathetic ophthalmia, were covered in previous reports.[1, 2] The features obtained in those studies were more typical of sympathetic ophthalmia than the ones obtained in this experiment.

With the later enucleations and larger doses used in this experiment, absorption of the infiltrate, fibrosis, and severe retinal necrosis were found in the injected eyes. Another feature of sympathetic ophthalmia has been simulated, however, and that is the production of an appreciable contralateral granulomatous uveitis.

Despite the similarity of the response to sympathetic ophthalmia there are two main points of difference.

1. First and foremost is the distortion, necrosis, and infiltration of the retinas in severely reacting injected eyes.

2. Second is the lesser degree of pigment phagocytosis.

B. Syphilitic uveitis. Except for the absence of perivascular infiltration and obliterating endarteritis, the reaction of the rabbit eye to horse serum bears a resemblance to a syphilitis uveitis. The same types of cells are present; the pigment epithelium is often destroyed; the retina is involved; and the infiltration is followed by organization.

C. Tuberculous uveitis. Characteristic features of tuberculous uveitis such as nodular infiltration, caseation necrosis, and anterior iris nodules, are not present in the reaction to horse serum, although some of the less distinctive features are seen.

D. Uveitis due to sarcoidosis. The main points of difference are that in sarcoidosis the anterior uvea is usually more affected than the posterior part, and the lesions disappear with little scarring. The main points of similarity lie in the presence of tuberclelike masses of epithelioid cells in injected eyes, and in the absence of caseation necrosis.

Summary

When the right eyes of rabbits were injected with normal horse serum and the rabbits were later given repeated large doses intravenously, a bilateral granulomatous uveitis developed in every case. The reaction was severe in the injected eyes and moderate in the uninjected. The tissue response consisted of an infiltration of the uvea by lymphocytes, large mononuclear phagocytes, plasma cells, and epithelioid cells. The injected eyes developed replacement fibrosis and involvement of the retinas; whereas, the infiltration in the uninjected eyes remained fresh and the retinas were not affected.

A second experiment was done in an attempt to elucidate the mechanism of the contralateral response. The rabbits of this second experiment received an original intracutaneous injection instead of a right intraocular injection but were otherwise treated in the same manner. It was found that both the clinical and microscopic reactions in the uninjected eyes of the first experiment were significantly greater than the reactions in the uninjected eyes of the second. The cause of this apparent superiority of the eye over the skin for the predisposition to a reaction in uninjected eyes was not learned.

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STIMULATION OF CORNEAL EPITHELIZATION WITH TOPICAL APPLICATION OF ERYTHROCYTES*

An experimental study

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A variety of chemical and physical agents has been recommended for topical application to stimulate wound repair but, after brief enthusiasm, almost all have been discarded as lacking the healing powers attributed to them. Hence it is with considerable diffidence that a report concerning yet another topical medication is submitted; however, compounds that accelerate the rate of corneal epithelization in experimental animals have been rarely reported and it is possible that local application of erythrocytes may have application in clinical ophthalmology.

Arey[1] in his comprehensive review of factors effecting wound healing mentions the following compounds reported at one time or another as stimulants to cell repair when applied locally. Vitamins A, C, and D, ergosterol and viosterol, testes pulp, thyroid, parathyroid extract, pancreas, insulin, suprarenal gland, anterior pituitary extract, leukocytes, embryonic tissue extract, Witte's peptone, and even irritants such as turpentine. Good results have been claimed for such physical agents as mechanical pressure, infrared, ultraviolet, and roentgen rays, phosphorescent light, and high-frequency electrical current. Hammett's[2] observation of the stimulating properties of certain compounds containing the sulfhydril radical prompted reports on the beneficial effect of thiocresol,[3] cysteine,[4] glutathione,[5] and more recently a proprietary preparation "sulfhydril solution."[6] Sperti[7] and his associates claim that "wound hormones," namely growth-stimulating substances released by damaged cells, initiate wound regeneration and accelerate healing. Recent well-controlled studies by Smith and Livingston[8] have indicated a stimulative factor in water-soluble chlorophyll preparations, while Werner[9] has used a heart extract in a large number of clinical cases with encouraging results. Marshak and Walker[10] have used a chromatin derivative extracted from rat liver to cause increased rates of healing of skin wounds of rats. Schaeffer[11] observed an increased rate of epithelization in experimentally abraded corneas treated with a buffered solution containing the amino acids, cysteine, proline, asparagine, and glutamine.

The multiplicity of compounds recommended for acceleration of wound healing indicates the chaotic state of the literature and one must consider with caution the claims advanced by frequently over enthusiastic investigators. In many of the earlier discussions, conclusions are founded on encouraging responses of the wounds to test agents as contrasted with the effects of medication used previously or after resistance to healing. Agents capable of stimulating tissue growth in culture or in experimental animals may have no similar action when applied locally in man. The cornea presents a singular problem in this regard as results derived from observation of skin healing cannot be applied in toto to corneal epithelization. In skin, wound repair is frequently by fibroblastic proliferation only; while in the cornea, restoration of normal epi-

* Read at the 16th scientific meeting of the Association for Research in Ophthalmology, Atlantic City, June 10, 1947. From the Department of Ophthalmology, Northwestern University Medical School. This investigation was supported in part by a grant from the Sanford R. Gifford Memorial Fund.

thelium is paramount and fibrous tissue formation is highly undesirable.

Moorhead and Unger[12] first employed concentrated human red blood cells as a wound dressing in 1943 and observed beneficial results in burns, infected and noninfected wounds, and certain types of ulceration. They suggested that erythrocytes might serve a useful purpose as a wound dressing in "raw and potentially infected surfaces." Seldon[13] and his associates found that local application of red blood cells stimulated healing in approximately one half of the cases of chronic ulcers. They recommended its use in ischemic ulcers and those associated with venous stasis. A number of other investigators have confirmed the initial report, but Naide,[14] after using whole blood, discontinued the use of erythrocytes believing that the plasma was more efficacious.

Experiment 1

This investigation was made to determine the effect of local application of concentrated, washed, human, red blood cells on experimentally produced corneal abrasions.

Technique

Freshly drawn citrated, human blood was centrifuged immediately following withdrawal and the supernatant plasma and buffy coat layer containing platelets and leukocytes was removed. The remaining erythrocytes were then washed four times with five times their volume of normal saline to insure removal of all plasma. After removal of the saline and concentration of the erythrocytes by centrifuging, the red blood cell count was 8 to 9 million per cubic millimeter. The test ointment was made by blending 5 cc. of the concentrated erythrocytes in 5 gm. of Hydrosorb ointment (Abbott*). This base was selected because of its lack of inhibition on the healing of the cornea as demonstrated by Smelser.[15]

Twenty-five immature, male, healthy guinea pigs weighing between 250 and 300 gm. were used. The animals were anesthetized with ether and a local ½-percent pontocaine solution. Using sterile precautions, the epithelium of a central corneal area, 4 mm. in diameter, in each eye was removed with a spatula.

Ointments were instilled in each eye four times daily at 8 A.M., 12 noon, 4 P.M., and 8 P.M. The erythrocyte ointment was used in the right eye, and the ointment base only in the left eye. Prior to the instillation of ointment, one drop of 2-percent fluorescein solution was placed in each eye and the eye was studied in intense illumination with a loupe. Healing was considered complete when the cornea did not stain.

Results

Eight of the 25 animals used were discarded because of corneal infection and were not considered in the final results. Of the remaining animals, the average healing time of the right, treated eye was 36.1 hours with a minimum of 23 hours and a maximum of 44 hours. In the left eye, the average healing time was 48.2 hours with extremes of 28 and 70 hours.

Analysis† of the results indicated that the acceleration of healing in the treated eye was statistically significant. It was concluded that local application of an ointment containing human erythrocytes

* A mixture of the oleic acid ester and the amide of diethanolamine in white petrolatum.

† To determine if the difference between the mean healing time of the two eyes was significant or due to chance, the standard deviation of the theoretical distribution of differences between the right and the left eye was determined. It was found that a difference as large as 8.8 hours (3 standard errors of the difference between the two means) might arise due to chance. In that the observed difference was 12.1 hours, it was concluded that the results were significant.

stimulated corneal epithelization in the guinea pig.

The method by which red blood cells exert this action is not known, but the complex physical and chemical structure of the erythrocyte and the unique metabolism of the cornea gives basis for wide speculation. Many of the compounds reported to stimulate healing of skin wounds are present in the erythrocyte. Thus, all of the glutathione in blood is present in the red blood cell and Kendall[16] was of the opinion that some chemical factor, possibly glutathione, was responsible for the effect. However, glutathione in 5-percent concentration in an ointment base does not stimulate corneal regeneration following abrasion in the guinea pig.[17]

Globin and ghost cells contain all of the essential amino acids and Murray and Shaar[18] suggested, on the basis of their clinical investigation, that erythrocytes might supply nutritional elements, possibly deficient because of inadequate circulation. They also suggested that the crust of erythrocytes served as a mechanical scaffolding to support epithelization. Heme, the iron prosthetic group of hemoglobin, is a ferriporphoryn chemically related to chlorophyll and other porphoryns which have been reported to accelerate healing. All of the amino acids used by Schaeffer[11] to accelerate corneal epithelization are present in the red blood cell but as polypeptides and proteins and presumably not available for use as such.

Baker[19] found that hemoglobin added to a mixture of liver ash and glutathione caused rapid proliferation of fibroblasts in vitro. She attributed this result to regulation of the oxidation-reduction reactions and respiration within the cells of the culture, and it is considered possible that a similar mechanism is responsible for acceleration of corneal healing activities.

Several investigators have attributed the healing action of erythrocytes, as observed in the treatment of stasis ulcers, to mechanical protection only. In that each eye in these experiments had comparable protection from the ointment base, it is concluded that such a factor is not responsible for acceleration of corneal epithelization in the eye. Carrell[20] showed that mild irritation of a wound initiated tissue regeneration while in the absence of chemical, mechanical, or bacterial irritation, healing was markedly delayed. However, sufficient irritation is ordinarily present in ocular wounds to initiate tissue regeneration and this mechanism seems highly improbable.

Experiment 2

To determine if a particular portion of the erythrocyte was responsible for the stimulation, an investigation was made using the primary products of mechanical and chemical fractionation of the erythrocyte; that is ghost cells, globin, heme, and hemoglobin.

Technique

Whole citrated blood, 10 to 15 days old, obtained from the Wesley Memorial Hospital Blood Bank, was used in all procedures. All manipulations, including centrifuging, were carried out at a temperature of 2°C., except as noted. The erythrocytes were separated from the plasma and washed five times with normal saline and refrigerated until used.

Ghost cells, the cell envelopes of the red blood cell with the hemoglobin removed, were obtained by adding to the washed erythrocytes five times their volume of water, saturated with carbon dioxide at 2°C. This hemolized and flocculated the cells which were then removed from the solution by centrifuging. The ghost cells were washed repeatedly with

cold, carbonated water until they assumed a light, pinkish color and the supernatant fluid was colorless. An ointment was made by blending 5 cc. of the concentrated ghost cells with 5 gm. of hydrosorb ointment.

Oxyhemoglobin was prepared by the method of Marshall and Welker,[21] first laking the washed erythrocytes with distilled water, mixing with freshly prepared alumina cream, and filtering in the refrigerator. The solution was sterilized by passage through a Berkefeld filter, and a test ointment was made by adding 5 cc. of the oxyhemoglobin solution to 3 gm. of ointment.

Globin and heme were prepared by the method of Anson and Mirsky.[22] Oxyhemoglobin was prepared as above and cold, distilled water added to 10 percent of its volume. To this solution was added an equal volume of 0.1 N. hydrochloric acid. The globin was precipitated by adding 20 times the volume of acid acetone and then separated from solution by filtration and dried in air. The globin was dissolved in distilled water, sterilized by passage through a Berkefeld filter, and an ointment prepared of equal parts saturated globin solution and hydrosorb.

Heme was precipitated from the acid acetone filtrate by acidifying with sodium acetate. It was then separated from solution by filtration. It was dissolved in bicarbonate buffer (pH = 10.1), sterilized, and blended into an equal amount of hydrosorb.

Five male, albino rabbits weighing between 2 and 3 kilograms each were used to test each ointment. Following ether anesthesia, the corneal epithelium of each eye was removed with dry gauze, and the eyes were stained with fluorescein to assure equal removal. Ointments were instilled four times daily, the test ointment in the right eye and the ointment base only in the left eye. Each cornea was stained with fluorescein prior to each installation of ointment, and the eye was studied in intense illumination with a loupe.

Results

Healing time in the treated and untreated eyes was between 4 and 6 days with no significant difference in the rate of healing of the eyes treated with ointments containing respectively globin, heme, oxyhemoglobin, and ghost cells, and the control eyes.

The failure of these erythrocyte products to accelerate healing may be explained in a number of ways. The initial possibility was that the stored blood used to prepare these products had lost some factor present in freshly drawn blood which was responsible for acceleration of wound healing. It was possible, however, to accelerate corneal regeneration using stored erythrocytes which indicated that living cells were not essential.

It seems most likely that the substance or substances responsible for the stimulation of healing were so modified in the separation process as to lose this power or were entirely removed and not represented in the final product. On the basis of these experiments, it seems probable that the proteins of globin and ghost cells are not responsible for stimulation of healing, and that the porphoryn radical of heme has no such action. Not disproved is the possibility of a synergistic mechanism whereby these substances exert a stimulative action when combined and not when separated.

Certain of the compounds removed in fractionation of the erythrocyte may be responsible for the acceleration of wound healing. Caspe[23] suggested that allantoin is responsible, but this compound seems more likely an end product of metabolism

rather than possessing metabolic activity. The erythrocyte contains a relatively large amount of adenosine triphosphate which may furnish the high energy phosphate bonds necessary for increased corneal metabolism accompanying acceleration of healing. The potassium ion in the red blood cell could catalize such an action. Coenzyme II which is present in significant amounts in the blood cell may catalize the above action or one of several others all of which would increase corneal metabolism.

Summary

Treatment of experimentally abraded corneas with an ointment containing washed, packed, human, red blood cells resulted in significantly increased rates of epithelization in the guinea pig.

Treatment with ointments containing ghost cells, heme, globin, and oxyhemoglobin, respectively, did not cause acceleration of corneal epithelization.

Possible mechanisms of this action are discussed.

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Discussion

Dr. Jonas Friedenwald (Baltimore, Maryland): I would like to ask what was the healing in eyes that were not treated at all, with any ointment. The question is asked because practically every ointment used in the eye delays healing to some extent, and I am wondering whether the favorable effect of the inclusion of red blood cells in the ointment might merely be neutralizing the inhibition of the ointment.

Dr. Frank W. Newell (Chicago, Illinois): I have not conducted experiments on eyes treated without ointments. I am afraid that I am not able to answer that question.

THE EFFECT OF DI-ISOPROPYL FLUOROPHOSPHATE ON THE CAPILLARIES OF THE ANTERIOR SEGMENT OF THE EYE IN RABBITS*

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The instillation of a 0.2-percent solution of di-isopropyl fluorophosphate into the conjunctival sac is usually followed in rabbits by a pronounced rise of ocular tension accompanied by edema of the ciliary processes and the formation of plasmoid aqueous. These changes indicate increased capillary permeability correlated with elevation of intraocular pressure. In the present study on the mechanics of this transient experimental glaucoma, the functional alterations of blood capillaries in respect to permeability† were investigated, as well as the prevention of these alterations by several groups of drugs. The occasional rise of tension in human eyes after topical use of D.F.P.‡ and especially the similarity of the test lesion to the human permeability glaucoma, added interest to the subject. Several aspects of the problem were examined using the rabbit as the experimental animal.

* Supported by the Knapp Memorial Foundation. From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology, Presbyterian Hospital. Read in part at the 16th scientific meeting of the Association for Research in Ophthalmology, Inc., at Atlantic City, June 10, 1947.

† The term capillary permeability is used in the present study irrespective of whether the changes in the rate of diffusion across the capillary wall were the result of altered pore size in the intercellular cement or of increase in filtration pressure.

‡ In a group of 50 glaucoma patients observed in the Institute of Ophthalmology, Presbyterian Hospital, five eyes with primary glaucoma responded to the use of D.F.P. with an increase instead of with the expected decrease in intraocular pressure. Leopold and Comroe[1] and McDonald[2] have previously reported a smaller incidence of such a reaction in a much larger series of glaucomatous eyes treated with D.F.P.

EXPERIMENTAL PROCEDURES

The rise of ocular tension, the protein content in the aqueous, and the depth of the anterior chamber after the local use of D.F.P.

The histologic appearance of the anterior segment of the eye under the influence of D.F.P. as described by R. O. Scholz[3] was confirmed in the present experiments. The changes consisted of swelling of the ciliary processes, development of Greeff blebs and appearance of a protein coagulate in the posterior and anterior chamber with some coating by proteins in the angle meshwork. They were especially striking when the eyes with heightened intraocular pressure after D.F.P. administration were compared to the untreated control eyes. Therefore, the relationship between protein content in the aqueous and the rise in tension was studied first.

TECHNIQUE

After tonometric determination of the ocular tension, 2 drops of an 0.2-percent solution of D.F.P. in peanut oil were deposited three times, three minutes apart, in the right eyes of adult chinchilla or albino rabbits. The changes in tension were recorded over periods of time from ½ to 5 hours and sometimes up to 24 hours. Many experiments were terminated after one hour by withdrawal of aqueous from the treated and the control eyes for protein determination by the Looney-Walsh method adapted for 0.1 cc. of aqueous as previously described.[4, 5] In a small number of experiments, the measuring of protein content was omitted.

These eyes were quickly frozen and cut in the vertical meridian and the depth of the anterior chamber in treated and control eyes was measured with a caliper under a 3× loupe magnification.

Results

The rise in tension became obvious 30 minutes after the instillation of D.F.P. and increased during the following hour; the tension then fell, but usually remained elevated for 4 to 6 hours. The degree of ocular hypertension varied greatly in individual animals. The maximum tonometer readings generally ranged between 30 and 50 mm. Hg, but measurements from 25 to 30 mm. and from 50 to 60 mm. Hg were also seen. The curve of Figure 1 illustrates the course of the tension changes based on 152 readings. The protein content in the aqueous was in general lower in eyes with moderate elevation of intraocular pressure and higher in eyes with greater hypertension, but the protein readings varied greatly in eyes with similar tension values. The protein concentration ranged, for example, from 200 to 1,450 mg. percent in the group having tension values of 40 to 60 mm. Hg. The aqueous of the control eyes showed an average protein level of 40 to 50 mg. percent which is on the high side of the range considered normal for rabbits.

The depth of the anterior chamber between the posterior surface of the cornea and the anterior pole of the lens was between 2½ and 3½ mm. depending on the size of the eye or the age of the rabbit. No clear or constant difference in depth was noted between eyes with high tension and untreated control eyes.

Comment

The data presented show that the connection between the increase in tension and protein concentration in the aqueous was slight, although there was a general indication that higher protein values were found more frequently in eyes with steeper and higher rises in ocular pressure. Recalling the marked edematous swelling of the ciliary processes with the development of Greeff blebs, one might conclude that the absolute height of the ocular tension was connected with filtration of water from the circulating blood into the extracellular tissue of the processes and into the chambers of the anterior part of the eye rather than with the passage of proteins.

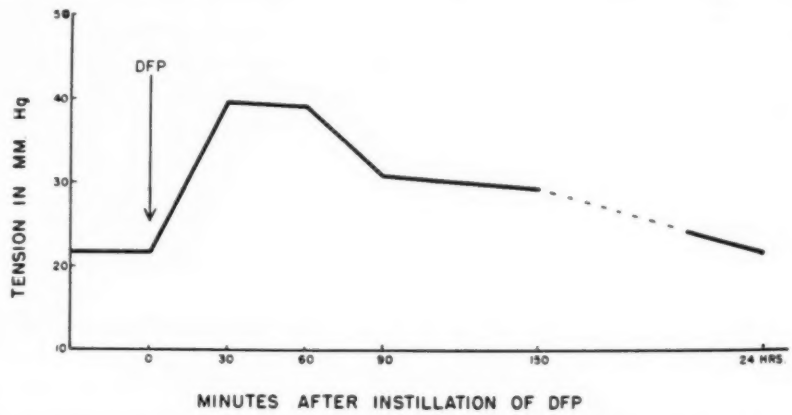
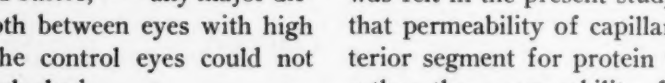


Fig. 1 (von Sallmann and Dillon). Changes in ocular tension after instillation of 0.2-percent solution of D.F.P. into conjunctival sac of rabbits.

The location of the swollen ciliary processes in rabbits between the peripheral part of the anterior surface of the lens and the posterior surface of the iris could conceivably influence the depth of the anterior chamber and the ocular tension in various ways. Although the accuracy of the measurements on frozen eyes compares unfavorably with the photographic method devised by Friedenwald and Pierce, and others,[6a, b, c] any major difference in depth between eyes with high tension and the control eyes could not have been overlooked.

Capillary permeability in the anterior segment of eyes after local use of D.F.P. studied with the blue Azo Dye T-1824.

The vital dye T-1824 with the supposed structural formula



was first recommended by Dawson, Evans, and Whipple,[7] for blood-volume determination. Gregersen, Gibson, and Stead,[8] using this dye, developed the method of measuring blood and plasma volume now widely employed. T-1824 in plasma or normal saline does not diffuse through cellophane membranes,[9] and does not pass the choroid plexus.[10] Its relatively low toxity[10–13] and its slow removal from the blood, observed by all investigators in this field, made the dye suitable also for studies of general capillary permeability in shock, and for changes of permeability in circumscribed areas. Such investigations were conducted by means of moat chambers in rabbit ears;[12] the increase of capillary permeability in experimental and human malignant neoplasms was in part established by the use of T-1824.[15, 11] Gregersen and Rawson[16] supplied highly suggestive evidence that, after intravenous injection, the dye becomes firmly bound to the serum albumin and that it escapes from general circulation in linkage with albumin. It appears to Gregersen and Rawson that this binding "is essentially equivalent to a tagging of albumin." The reasons for this assumption will be outlined in the discussion. On this basis, it was felt in the present study with T-1824 that permeability of capillaries in the anterior segment for protein was examined rather than permeability for a colloidal dye.

TECHNIQUE

Thirty minutes after the repeated instillation of a 0.2-percent solution of D.F.P. in one eye of albino rabbits, the dye, dissolved, prepared, and autoclaved according to usual rules, was injected in one of the lateral ear veins in a dose of 20 mg. per kilogram. The permeation of the colored substance from circulating blood into the tissue and fluids of the anterior part of the eye was observed by transscleral transillumination and biomicroscopically. For permanent recording, a great number of Kodachromes were taken of various stages of permeation of the dye in eyes treated with D.F.P. and in the control eyes. At the end of the observation period, the tension was measured, the aqueous withdrawn for protein determination, and the eyes dissected to allow direct inspection of the ciliary processes. Their staining in the treated and control eyes was also photographed in color. Finally the iris and ciliary body were removed,

fixed in acetone, embedded in paraffin, sectioned, and studied microscopically without additional staining.

In a group of three animals, the cytochrome oxydase of the ciliary epithelium was inhibited by cyanide iontophoresis in one eye with the technique previously reported.[17] The D.F.P. solution was instilled in both eyes 20 minutes later. This procedure was followed after 20 minutes by intravenous injection of the dye. The changes in the caliber of the vessels and the appearance of the dye compound in the anterior portion of the eye was observed in the usual way.

Three albino rabbits serving as controls were injected in the same manner with T-1824 without preceding treatment with D.F.P. or tonometric measurements. The animals were killed after one hour by intravenous injection of a 2-percent solution of sodium pentobarbital, then the eyes were removed without exerting undue pressure and were dissected in a frontal plane about 3 mm. behind the limbus. The vitreous and lens were gently removed and the posterior surface of the ciliary body and the iris were exposed for examination with the loupe or wide-angle microscope and for color photography.

Results

In control animals, no trace of dye was seen outside the vessels of the limbus and iris when examined with strong light and loupe magnification or under the 30× enlargement of the corneal microscope. There was a light blue coloration of some ciliary processes, which indicated slight permeability of ciliary capillaries for the dye-protein complex in untreated eyes. Staining of several ciliary processes was somewhat more marked in the eyes of a young animal weighing less than 2 kg. No dye was seen in the primary aqueous.

Similar results were observed in the control eyes of rabbits receiving D.F.P. treatment on the contralateral eyes; that is, no dye passed through the walls of the limbus and iris vessels into the tissue. However, many ciliary processes showed a light-blue staining which did not extend into the tissue of the iris. The aqueous was apparently free of dye.

The eyes on which D.F.P. had been

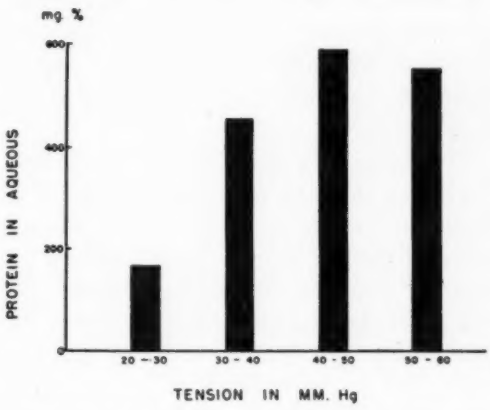


Fig. 2 (von Sallmann and Dillon). Protein content in aqueous and ocular tension one hour after instillation of D.F.P. in rabbits.

used prior to the injection of the dye had dilated limbal vessels and distended iris capillaries, mostly in the pupillary part, but no permeation of the colored substance through the walls of these dilated vessels occurred. On the other hand, under transscleral transillumination, a progressively more intense staining of the ciliary processes became visible, followed within five minutes by the appearance of blue lines in the iris. They were not related to the vessels of the iris, but clearly signified the spreading of the colored material from the ciliary processes along their insertions at the posterior surface of the iris. The blue lines later lost their sharpness as the dye complex diffused into the iris tissue and escaped from its anterior surface into the aqueous. At a later stage, a dark-blue stained aqueous emerged from the posterior chamber

through the pupil into the anterior chamber. All these changes could be seen macroscopically and were well demonstrated by color films.

The inner surface of the ciliary body and of the iris showed a homogeneous deep-blue ring corresponding to the corona ciliaris. The accumulation of dye in the processes outside the vessels was so abundant that no attempt was made to examine for a gradient of vascular permeability along the arterioles, capillaries, and venules in the sense of Rous and Smith.[18]

The primary aqueous of the eyes which had been instilled with D.F.P. showed a light blue color about 30 minutes after the injection of the dye. The intensity of the dye could not be estimated either by the common slitlamp technique or with the addition of filters. It could only be estimated on withdrawn samples, and in these the concentration of dye and protein in the aqueous seemed roughly proportional. Spectrophotometric measurements of the optical density values in the small amount of aqueous available (0.1 cc. was used in protein measurements) were not attempted in this study.

Several phases of the diffusion of T-1824 from circulating blood into the tissue of the ciliary processes could be distinguished microscopically on unstained sections. First the interstices of the ciliary processes appeared homogeneously tinted, occasionally with a moderately more intensive staining of the vascular wall. Thirty minutes after injection, the colored material was seen in many processes in the form of blue bands underneath the covering layers of epithelium. In several instances, the dye was later visible within the epithelial layers. There was no evidence, however, that the dye had entered the cytoplasm of the cells. Two hours after the injection, a few histiocytes in the processes contained blue granules. Later stages were not examined.

The diffusion of the dye into the structures of the ciliary processes and iris and into the aqueous occurred in the same way in eyes which had been treated with cyanide iontophoresis and D.F.P. instillations as in eyes in which D.F.P. had been used alone. The banking of the colored substance underneath the epithelial layers was also similar to that of the control eyes. As far as can be judged from fixed preparations, the inhibition of the indophenol oxydase in the ciliary epithelium apparently did not change the permeation of the dye from the blood into the tissues and chambers of the anterior part of the eye.

Comment

Gregersen and Rawson[16] explained the slow escape of T-1824 from the blood, which greatly exceeded the disappearance rate of structurally related diazo dyes by its combining with proteins. The nature of the linkage is not known. Rawson and Moore[19] showed in electrophoresis experiments that the dye was wholly bound by the albumin fraction of the serum up to a molar concentration of 10:1; that is, 1 mole albumin may combine with as many as 10 moles of T-1824. The affinity to albumin markedly surpassed that of trypan blue and niagara sky blue as concluded from the results of Rawson's cellophane staining test. No dissociation of the dye-albumin compound occurred in the electrophoretic cell or in ultracentrifugation where the dye came down with the albumin.

In general the histologic examination of the ciliary processes of albino rabbits did not reveal, in the early phases, a preferential binding to constituents of the plasma membrane, the cytoplasm of cells, or other tissue elements. The appearance of protein and dye in the Greeff blebs and

the roughly proportional content of dye and protein in the aqueous strengthened the impression that a splitting of dye from protein did not occur during the permeation from the blood through the membranes of the blood-aqueous barrier, and that the dye-albumin complex passed into the aqueous as a whole. From the already mentioned binding capacity of albumin, it can be seen that the amount of dye injected fell far below this value.

In normal undisturbed rabbits' eyes, a small amount of the colored material entered from the blood into the tissue of a few processes. In view of the relatively low toxity of the dye this would indicate that the ciliary capillaries of rabbits possess a moderate degree of protein permeability. It is known that the physiologic impermeability of the capillary wall to protein is not uniform in various areas of the peripheral circulatory system, and it has been shown with other colloidal dyes that under pathologic conditions the capillaries of the ciliary processes are more permeable than the capillaries of the iris. Such a gradient of permeability between limbus and iris and ciliary capillaries could be observed in the present study in the untreated eye, but much more convincingly by dilating the vessels of these three systems in the anterior portion of the eye by means of the anticholinesterase D.F.P. The retention of the dye complex by the wall of the limbus and iris capillaries was not changed in the state of dilation. It is interesting that Rocha e Silva and Dragstedt[20] and others could not produce a positive trypan blue reaction by injecting acetylcholine intradermally in an abdominal area of rabbits. Similarly, Last and Loew[21] did not observe increased capillary permeability tested with this method in the rabbits' skin by substituting the longer acting acetyl-methylcholine for acetylcholine.

The blue color of the dye T-1824 which proved beneficial in measurements of blood volume was also of advantage in the study on eyes of albino rabbits. Certain difficulties in the interpretation of experiments with fluorescein were eliminated by the use of T-1824, as its initial diffusion from the circulating blood into the loose tissue of the ciliary processes, its spreading into the iris, the escape from the iris surface into the aqueous, and the outpouring of dark blue aqueous from the posterior chamber through the pupil could be readily demonstrated.

The local action of D.F.P. on the vessels of the limbus.

The dilation of the vessels in the anterior part of the eye and the pronounced increase in permeability of the ciliary vessels to protein was supposedly elicited in the present experiments by the intensified action of the undestroyed cholinergic chemical mediator. It was not clear how this effect was brought about or where the point of attack lay. To our knowledge, no work on the pharmacology of D.F.P. has been reported in regard to its local action on vessels. On the other hand, the innervation of finer branches and the intimate anatomy of the functional unit of the capillary bed—capillary-metarteriole-venule—in the anterior portion of the eye, has not been studied sufficiently. Observations of the limbus vessels under a 30-fold magnification of the corneal microscope supplied several suggestive data on the local action of D.F.P.

TECHNIQUE

In an area of the limbus of one eye of albino or chinchilla rabbits which could be well exposed under the corneal microscope, the distribution and relative calibration of small arterioles, capillaries, and veins were outlined in a sketch. Then a 0.2-percent solution of D.F.P. was instilled into the conjunctival sac and the

sequence of caliber changes of various parts of the vascular net was registered. After 15 minutes, the minimal effective dose of epinephrine for closure of capillaries was determined on the eye which had received the D.F.P. drops as well as on the contralateral control eye. The caliber changes of the vessels in the selected area of the limbus were again outlined and compared to those observed after the use of D.F.P. Photographic records could not be obtained.

Results

The dilation of the limbus vessels was noted within 10 minutes after several drops of the D.F.P. solution had been employed. The diameter of arterioles, metarterioles, and capillaries increased about the same time. No premature distention of capillaries preceding the hyperemia of arterioles was seen. Under the conditions of the experiments, it could not be decided whether the region of the precapillary sphincter itself responded synchronously with the arterioles.

The concentration of the minimal dose of epinephrine hydrochloride necessary for marked constriction of the vascular tree and closure of some capillaries was 1:500,000 to 1:1,000,000, when several drops of this solution had been deposited in the conjunctival sac. This dose had to be increased 20 to 100 times, that is to about 1:10,000 for a comparable constriction of the terminal branches of the limbus vessels of eyes under the influence of D.F.P. The narrowing of the capillaries took place simultaneously with the great reduction in the size of the diameters of the arterioles and metarterioles.

Comment

In general, the technique of Chambers and Zweifach[23] and Zweifach[22] devised for the mesentery capillaries of rats was applied in the epinephrine experiments. The magnification which these authors could utilize for their examination of the vessels in the meso-appendix was at least three times greater and the conditions for accurate observations were by far more favorable than those in the experiments on the limbus vessels of rabbits. Here it was impossible to identify structural details such as the location of Tannenberg's[24] "Pfoertner Zellen" or the precapillary sphincter, and to judge the sensitivity of this area to effective threshold concentrations of epinephrine in comparison with the sensitivity of arterioles or metarterioles.

Capillaries and arterioles changed in caliber at about the same time both in dilation after use of D.F.P. and in constriction induced by subsequent instillation of epinephrine hydrochloride (1:10,000). These results suggest that accumulated acetylcholine acted on the neuromuscular junction of the arterioles and that the induced dilation of these branches with its augmented blood flow led immediately to a passive filling of the capillaries. This concept is in line with the widely accepted opinion[22, 25, 26] that the filling of mammalian capillaries and venules follows passively the dilation and contraction of the supplying arterioles.

The influence of drugs on the increased capillary permeability induced by the use of D.F.P.

The signs of increased capillary permeability including elevation of intraocular pressure in the test lesion could be variously influenced by drugs. In these experiments changes in tension, in protein content of the aqueous, in diffusion of the dye T-1824, and in size of the pupil were observed and correlated. Four groups of pharmaceutics were examined: (1) adrenergic compounds, (2) pituitrin (3)

a calcium salt and adrenal cortex extract, and (4) histamine antagonists. The measurements of protein content in the aqueous and the use of the dye followed the technique previously described. Variations in timing of the experiments and in application of the drug will be dealt with separately in the individual sections.

1. Adrenergic drugs

Technique

Epinephrine and neosynephrin were tested. Epinephrine hydrochloride, 0.1 cc. of a solution (1:1,000), was injected subconjunctivally underneath the superior rectus muscle of the right eye 20 minutes prior to repeated instillations of the solution of D.F.P. in both eyes. One drop of the emulsion of neosynephrin hydrochloride, 10 percent, was deposited three times in the right eye 30 minutes before or 10 minutes after the use of the D.F.P. solution in both eyes. In the experiments in which the use of neosynephrin preceded that of D.F.P., three drops of the blank vehicle were applied in the left eye. The measurements of the pupillary diameters were made with a pencil flashlight at a distance of one foot.

Results

The subconjunctival injection of epinephrine hydrochloride on the right eye prior to treatment of both eyes with D.F.P. prevented the rise in tension of this eye. The differences of the tension values between the two eyes were consistently greater 30 minutes after the last instillation of D.F.P. drops. At this time the averages of 10 experiments were 18.3 mm. Hg, right eye, and 43.5 mm. Hg, left eye. Ninety minutes after the use of D.F.P. the respective values of seven experiments read: 16.7 and 25.9 mm. Hg, and in the three eyes which were measured 150 minutes after employment of D.F.P., 22 and 29.3 mm. Hg. The protein readings in the aqueous of six rabbits at the 90-minute interval showed averages of 354.4 mg. percent, right eye, and of 643.7 mg. percent, left eye. In the albino rabbits, which had received the dye T-1824 intravenously with the usual technique, the right iris remained unstained. After dissection of the eyes, the right ciliary processes were considerably less blue than in the control eyes and were often unstained in the upper medial sector corresponding to the area of in-

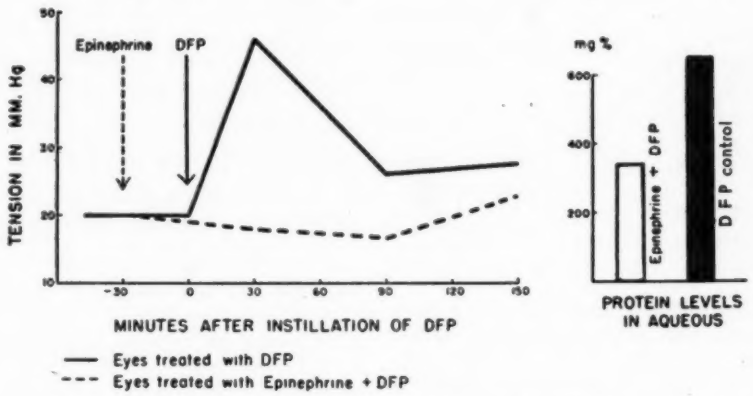


Fig. 3 (von Sallmann and Dillon). Changes in ocular tension and protein levels in the aqueous after instillation of D.F.P. preceded by subconjunctival injection of epinephrine hydrochloride (0.1 cc. 1:1,000 dilution) in one eye.

jection. Thirty minutes after the use of D.F.P., the diameter of the right pupil measured from 3.5 to 5 mm. while the average diameter was 1 to 2 mm. in the control eyes.

Neosynephrin-hydrochloride emulsion applied to the right eye before the use

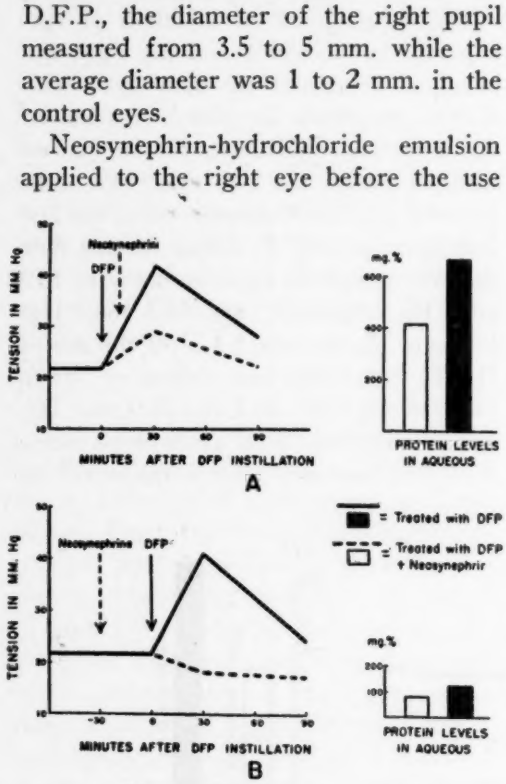


Fig. 4 (von Sallmann and Dillon). Changes in ocular tension and protein levels in the aqueous after the instillation of D.F.P. (A) followed by instillation of neosynephrin-hydrochloride emulsion (10 percent); (B) preceded by neosynephrin-hydrochloride emulsion (10 percent).

of D.F.P. counteracted the effect of D.F.P. on the intraocular pressure. The tension values after 30 minutes were: R.E., 17.5 mm. Hg, and L.E., 42.3 mm.; and after 90 minutes: R.E., 17 mm. Hg, and L.E., 24 mm. (average of four experiments).

The protein in the aqueous measured less than 80 mg. percent in the right eye and 111 mg. percent in the left. The aqueous of the eyes treated with neosynephrin was not colored and the ciliary processes were stained only light blue. The size of the pupil differed less from the size in the control eyes (3 to 4 mm.; 1 to 2 mm.) than in the epinephrine experiments.

The instillation of neosynephrin 10 minutes after the use of D.F.P. influenced the tension to the following extent—after 30 minutes: R.E., 29.3 mm. Hg; L.E., 41.8 mm.; after 90 minutes: R.E., 22.5 mm. Hg; L.E., 27.5 mm. (average of four experiments). The protein measurements in the aqueous gave an average of 337 mg. percent in the right eye and 532 mg. percent in the left. This series did not contain tests with T-1824. The relation of the pupillary diameters of both eyes was comparable to that in the preceding experimental group.

Comment

It is obvious that the two adrenergic compounds eliminated the elevation in tension, occurring in rabbits after the use of D.F.P., when they were administered prior to or after the instillation of D.F.P.

The curve of rising tension in the control eye did not deviate from the average standard curve (fig. 1) at the 30 minute interval, but declined rapidly thereafter, so that values below 30 mm. Hg were reached after 90 minutes. This early decline of the tension curve suggested absorption of the sympathomimetic compound from the conjunctival sac of the treated right eye into the general circulation, affecting the other eye. The comparatively small difference between the protein reading in the aqueous of both eyes (especially in the experiments with neosynephrin—first group) can also be interpreted in the same way. The results of the dye experiments did not contribute to answering this question since quantitative measurements of the optical density in the aqueous were not carried out.

The use of epinephrine or neosynephrin greatly interfered with the con-

striction of the pupil due to D.F.P. The dilation of the pupil in this combined treatment must be considered a hazard already experienced in a few instances of human chronic glaucoma with high tension, which did not respond favorably to local medication with D.F.P. The addition of epinephrine base, dissolved in oil, led to a further widening of the pupil and subsequent rise in tension.

Thirty minutes later the tension was recorded, and the D.F.P. solution was instilled in one eye in the experiments with systemic injection or in both eyes of rabbits which had received the topical treatment unilaterally.

Results

Intramuscular injection of pituitrin caused a drop in tension of untreated

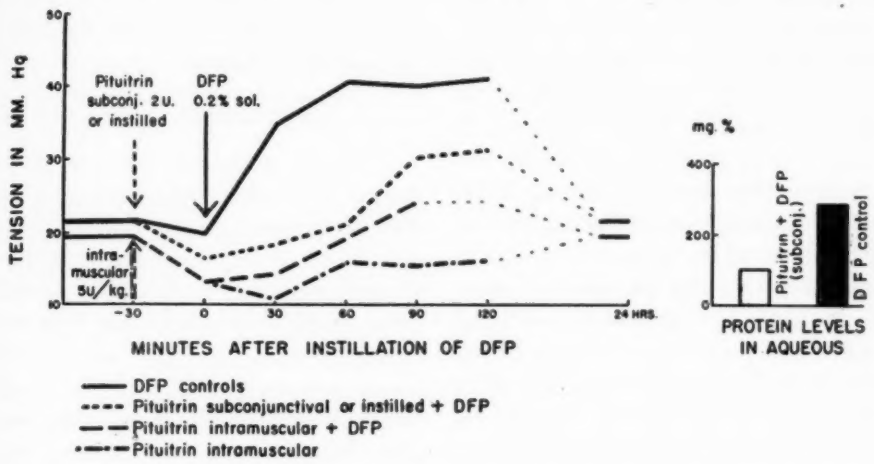


Fig. 5 (von Sallmann and Dillon). Changes in ocular tension and protein levels in the aqueous after the instillation of D.F.P. preceded by instillation, subconjunctival or intramuscular injection of pituitrin.

2. Pituitrin

The effect of posterior pituitary preparations was studied with the Parke Davis product, which contains 20 international units per cc. The drug was administered by the systemic route or topically on untreated eyes and on eyes under the influence of D.F.P.

Technique

The tension was taken prior to any medication. The pituitrin preparation was injected intramuscularly in a dose of 5 units/kg. or under the conjunctiva in one eye in a dose of 2 units. In a few instances the solution was instilled into the conjunctival sac instead of being injected.

eyes from 19.3 mm. Hg to 10.5 mm. after one hour and to 15.5 mm. after 150 minutes* (averages of six experiments). It overcompensated the effect of D.F.P. for one hour with average readings of 14 mm. Hg, rising to 24 mm. after two hours.

The initial tension of 21.8 (six experiments) decreased to 16.3 mm. Hg, 30 minutes after the subconjunctival injection of 2 units; the tension of the other eye was not changed at this time. In 18 eyes with an average initial tension of 19.5 mm. Hg, the heightening of tension after use of D.F.P. was eliminated for 90 minutes (average readings after 30 minutes 18.3 mm. Hg and after 90 minutes 20.8 mm.). In these experiments

with the topical use of pituitrin the measurements of the protein content in the aqueous revealed a ratio of 66.7 to 283.3 mg. percent (average of four experiments) for the eyes treated with pituitrin and D.F.P. and the eyes treated with D.F.P. respectively. The instillation of the pituitrin gave results like those obtained with the local injection.

In the dye experiments the difference in the intensity of staining of aqueous, iris, and the ciliary processes between the two groups of eyes was very marked; that is, the aqueous was unstained, the iris showed no escape of the dye, and the ciliary processes were tinted much less than those of the control eyes, especially in the upper medial sector. When the anterior chamber of both eyes was emptied 150 minutes after the injection of pituitrin in the right eye, the secondary aqueous was almost unstained in contrast to the very dark-blue colored aqueous which filled the anterior chamber of the left eye.

The subconjunctival injection of pituitrin prevented the maximal constriction of the pupil observed after use of D.F.P., but the difference between the two eyes was markedly less (2-3 mm.: 1.5-2 mm.) than in the experiments with epinephrine or neosynephrin.

Comment

The systemic and local uses of pituitrin were beneficial in blocking the action of D.F.P. on the tension of rabbits' eyes. The protein readings in the aqueous and the observations with the dye indicated that the prevention of ocular hypertension was connected with the vasoconstricting effect of the hormone which lasted several hours as shown best in the formation of an almost colorless secondary aqueous 150 minutes after the local use of pituitrin. The comparison of the protein concentrations in the aqueous and of the changes in ocular pressure of the eyes treated with pituitrin and D.F.P. with those treated with D.F.P. alone pointed again to systemic absorption of the hormone from the depot beneath the conjunctiva. This assumption explained the difference of values in control eyes of this series from averages obtained in rabbits on which only D.F.P. was used. It might be of practical importance that the topical use of pituitrin secured the full effect on the permeability of the ciliary capillaries with only moderate inhibition of the D.F.P. miosis.

3. Calcium. Adrenal cortical extract

It has been stated that any procedure which alters the physicochemical properties of the intercellular cement affects the rate of filtration across the capillary wall. Chambers and Zweifach[23] demonstrated with an elaborate technique that calcium-free perfusion fluid at a slightly acid pH rendered the capillary wall leaky by softening and washing away the intercellular cement, and that doubling the normal amount of calcium in the fluid caused overproduction of the cement material. This experimental evidence concerning the importance of the calcium concentration in the perfusate for the filtration across the capillary wall was the basis for investigations on the effect of a calcium salt variously introduced in eyes in which protein permeability of the ciliary capillaries had been increased by instilling D.F.P. solution in the conjunctival sac.

The use of adrenal cortical extract was considered in view of the studies of Swingle, Parkins, and Remington,[27] Menkin,[28] Freed and Lindner,[29] and others, in which the integrity of the peripheral vascular system and the maintenance of normal capillary permeability was shown to be controlled in some way by the adrenal cortex. There is no experimental evidence that the extract influences capillary permeability by changing physical condi-

tions of the intercellular cement, but the possibility of such a mechanism cannot be ruled out.

TECHNIQUE

A. Calcium. Calcium gluconate, 10 percent (pH 5.5),* was either injected under the conjunctiva (0.2 cc.), introduced by anode corneal iontophoresis (1.5 ma. for 5 minutes), or given intravenously (5 cc. per kg.). D.F.P. instillations on both eyes followed the local procedures after 30 minutes and preceded the systemic introduction by 10 minutes.

RESULTS

The subconjunctival use of calcium salt on the right eye caused severe chemosis and did not noticeably alter the rise in tension after use of D.F.P. (average of four experiments: R.E., 56 mm. Hg; L.E., 60 mm.). When calcium iontophoresis was employed on the right eye 30 minutes before depositing D.F.P. drops in both eyes, tension curves of both eyes reached almost the same levels one hour after the D.F.P. medication (average of six experiments: R.E., 34 mm. Hg; L.E., 39 mm.). Four experiments with the intravenous injection of calcium gluconate, followed after 10 minutes by the use of D.F.P., showed rise in tension to an average of 50 mm. Hg (four experiments). In the iontophoretically treated eyes the protein level in the aqueous slightly exceeded (average of 613 mg. percent) that of the control eyes (average of 536.3). The diffusion of the dye T-1824 and the constriction of the pupil caused by the use of D.F.P. were not essentially changed under the treatment with the calcium salt.

B. Adrenal-cortex extract. The study was limited to the use of one preparation of whole cortical extract (Upjohn), which contained 50 dog units or 2.5 rat units per cc. The intravenous route was selected in two series. After measuring the tension of both eyes, 0.5 cc. per kg. of extract (25 dog units) was injected and the changes in intraocular pressure were followed over a period of 24 hours without any other treatment. In another group of animals the protein concentrations in the aqueous were determined 90 and 120 minutes after the experiment was begun and were compared with those of untreated rabbits which had been subjected to similarly timed tonometry. In a second series three drops of the D.F.P. solution were placed in one or both eyes 15 minutes after injection of the extract. Tonometric readings were obtained 30 minutes to 24 hours after instillation of the D.F.P. solution. T-1824 was used only in a few instances.

A small group of rabbits was treated by injection of 0.05 cc. of extract under the conjunctiva; 30 minutes later the D.F.P. solution was applied and the tension was determined after 30, 90, 150 minutes, and 5 hours.

RESULTS

The intravenous use of adrenal cortex extract in otherwise untreated animals was followed by a gradual lowering of the ocular pressure to a minimum reached six hours after injection. The average difference between the readings taken before the injection and the values six hours later was 7 mm. Hg (nine experiments). Massage effect of the tonometric procedure was improbable since in control experiments such a response was absent when tonometric measurements had been repeated at hourly intervals. The tonometry on untreated rabbits' eyes apparently caused some irritation which led in several instances to an increase of protein content in the aqueous; in one instance

* Neo-calglucon, Sandoz Chemical Works, Inc., was used.

it reached 196 mg. percent. This effect was not evident in eyes of rabbits which had received the injection of adrenal-cortex extract. Here the average of the protein content of 10 eyes was 42.7 mg. percent.

The rise in tension due to the use of D.F.P. was not greatly influenced by treatment with adrenal-cortex extract.

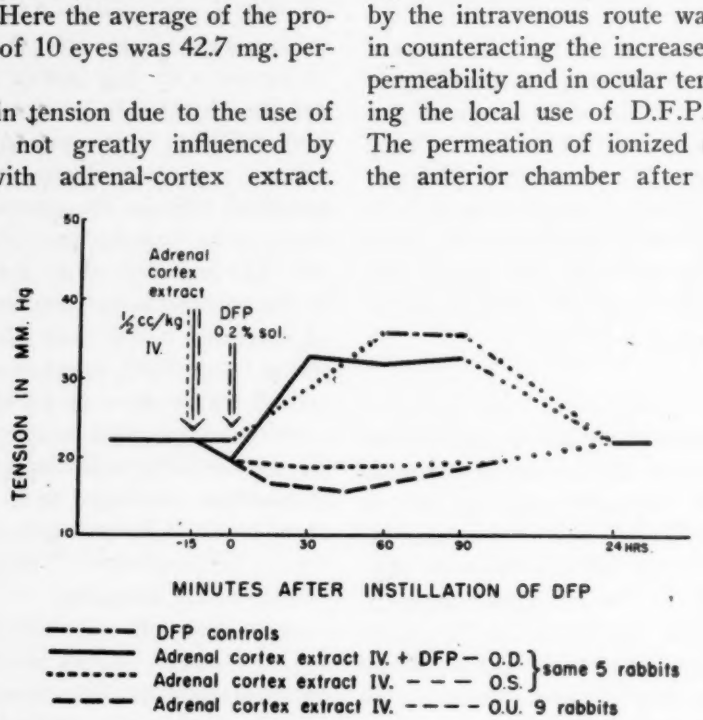


Fig. 6 (von Sallmann and Dillon). Changes in ocular tension after instillation of D.F.P. preceded by intravenous injection of adrenal-cortex extract (Upjohn).

The tension rose from a base value of 23.8 mm. Hg to maximal values around 32.4 mm. in the first 90 minutes and fell to 26.5 mm. Hg after five hours (five rabbits). The control eyes of these rabbits not treated with D.F.P., exhibited a decrease in tension of about 5 mm. Hg. In a simultaneously observed control group of rabbits (four eyes) which were only under the influence of topical D.F.P. applications, the tension increased to an average of 36 mm. Hg. Subconjunctival injection of the hormone preparation in one eye, succeeded by the use of D.F.P. on both eyes 30 minutes later, failed to prevent increase of ocular pressure in two instances and was questionably beneficial in two other instances.

Comment

Calcium gluconate introduced by iontophoresis, subconjunctival injection, or by the intravenous route was ineffective in counteracting the increase in capillary permeability and in ocular tension following the local use of D.F.P. in rabbits. The permeation of ionized calcium into the anterior chamber after topical surface application so far has not been determined. It will be necessary to augment the number of observations and to modify the experimental procedure before any broader evaluation of the effect of calcium on the ciliary capillaries is permissible.

It is not known how the adrenal cortical extract acts on capillary permeability, and direct observations on the influence of adrenal steroids on capillaries are sparse. Menkin,[28] and Freed and Lindner[29] noticed reduced filtration of trypan blue from the circulating blood into areas of skin injected with leukotaxin after cortical substances had been added to the toxin. Fine and Fischmann,[30] using desoxycorticosterone acetate, confirmed the decrease in the rate at which various dyes

leave the capillaries of the rabbit's ear under the influence of the synthetic product but thought that this effect on the diffusion of the dye was not related to an alteration in capillary permeability. Hyman and Chambers[31] observed that whole cortical extract added to the perfusion fluid in a dilution of 10^{-8} reduced the rate of edema formation in the frog's hind limbs; the authors were unable to conclude, however, whether this effect was due to a change in capillary permeability. If their results are taken to indicate such a change, an influence of the hormone on the tonus of the capillary endothelium (Chambers[32]) or on adsorption of proteins at the intercellular cement (Zweifach[33]) could offer an explanation for the phenomenon. At this stage of the investigation no conclusion can be drawn concerning the mechanism by which the cortical extract, injected intravenously, lowered the ocular tension in undisturbed rabbit eyes and prevented the rise of protein content of the aqueous in eyes irritated by repeated tonometry. Further studies are warranted.

4. HISTAMINE ANTAGONISTS

Local mechanical stimulation, lack of oxygen, or any kind of injury may cause considerable transudation of fluid from the blood into the tissue due to increase in capillary permeability. It has been thought that under such conditions the liberation of histamine or a special H substance may give rise to capillary dilation and sometimes to increased permeability. Although the validity of this theory was questioned (Menkin[34]), the possibility of activating an histamine mechanism by stimuli, such as stretching of tissue or rapid increase of the tissue pressure, cannot be excluded. From this viewpoint, the experiments on the effects of drugs on the test lesion under consideration were extended to several histamine antagonists. Three representatives of this group were selected: benadryl (β dimethylaminoethyl benzhydryl ether), hydrochloride, pyribenzamine (N′-benzyl-N′-dimethylaminoethyl aminopyridine) hydrochloride, and antistine (2 [N-phenyl-N-benzyl-aminomethyl] imidazolin) sulphate.

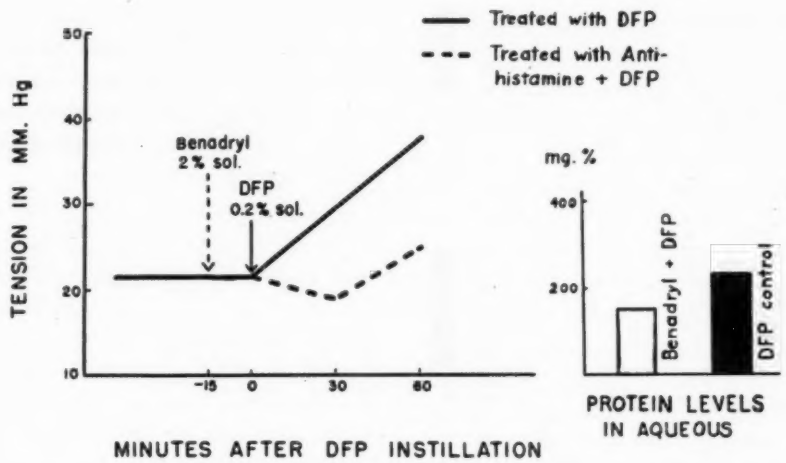


Fig. 7 (von Sallmann and Dillon). Changes in ocular tension after instillation of D.F.P. preceded by instillation of benadryl-hydrochloride solution (2 percent).

Technique

The compounds were applied topically only by instillation since subconjunctival injections caused considerable irritation. Two drops of a 2-percent solution were deposited in the conjunctival sac, three times, at 3-minute intervals in all experiments. Fifteen minutes later the solution of D.F.P. was used on both eyes. In conformity with the procedure in the case of other drugs, the tension was taken before treatment was initiated and 15 minutes later; that is, immediately before the employment of the D.F.P. solution. The changes in tension were then followed over a period of 90 minutes and the protein content was determined at the end of this period. In connection with these studies pooled aqueous of eyes pretreated with D.F.P. was tested pharmacologically for histamine activity on the isolated gut of the guinea pig.*

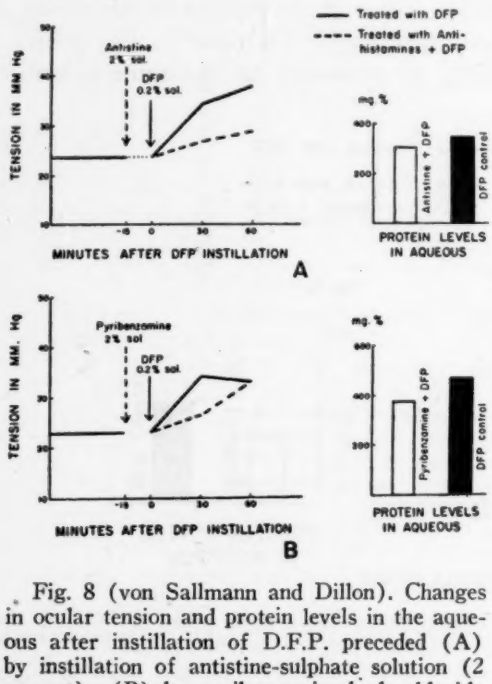


Fig. 8 (von Sallmann and Dillon). Changes in ocular tension and protein levels in the aqueous after instillation of D.F.P. preceded (A) by instillation of antistine-sulphate solution (2 percent); (B) by pyribenzamine-hydrochloride solution (2 percent).

Results

A. Benadryl hydrochloride. One hour after the instillations of the solution of D.F.P., the tension average on the right eyes treated with benadryl and D.F.P. was 24 mm. Hg, on the left eyes treated with D.F.P. alone, 38 mm. Hg (averages of four experiments). The protein concentrations in the aqueous of the right eyes were scattered from 60 to 305 mg. percent and on the left eyes from 60 to 411.4 mg. percent. The difference in the averages (right eye 150, and left eye, 200) cannot be considered significant. The diffusion of T-1824 was delayed in both eyes and moderately more marked in the eyes which had not received benadryl. The pupils of these eyes were relatively dilated when compared with the control eyes (3.4 to 1.2 mm.).

B. Pyribenzamine hydrochloride. The use of this compound did not prevent the tension rise from a base value of 22.8 mm. Hg to 33.7 mm. after one hour (three experiments); the control eyes showed at this time a similar elevation of 36 mm. Hg. The average protein level in the aqueous of the treated eyes was 376 mg. percent when the histamine antagonist was used and 470 mg. percent in the control eyes. Corresponding to these readings, the permeation of the dye was less pronounced in the eyes treated with pyribenzamine. The pupils of these eyes contracted less than in eyes on which D.F.P. had been used alone (3 to 4 mm. right to 1 to 2 mm. left).

C. Antistine sulphate. The tension of eyes treated with antistine and D.F.P. showed an average increase from 23 to 29 mm. Hg one hour after instillation of D.F.P. solution. Control eyes on which D.F.P. alone had been used gave an av-

* These experiments were conducted by Dr. A. Gellhorn of the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

erage reading of 38 mm. Hg (four experiments). The group of eyes under direct influence of both substances contained 301.8 mg. percent protein, the control eyes 352.5 percent. The intensity of the blue staining also differed from rabbit to rabbit. Usually the diffusion occurred earlier and was greater in the eyes treated with D.F.P. only. In contrast to the two other drugs of this group, antistine did not interfere with the development of the D.F.P. miosis.

When the aqueous of both eyes of five rabbits was withdrawn and pooled 2, 4, and 18 hours following the treatment with D.F.P. (three experiments on 15 rabbits) and amounts of aqueous (up to 1 cc.) were added to a gut preparation in 10 cc. of oxygenated Tyrode solution, no contraction of the gut was observed. A 0.5-cc. solution containing 1.0 γ per cc. of histamine diphosphate and 0.5 cc. of an 0.000005 molar solution of acetylcholine caused intensive contraction of this preparation. It was concluded that these substances, when present in the aqueous, did not reach the effective threshold level.

Comment

The new antihistamine drugs possess, besides their main action and anesthetic properties, a parasympathicolytic side action and the ability to potentiate adrenergic responses.[35–39] The quantitative relation between these individual actions varies with the different compounds. Although the ineffectiveness of pooled aqueous of eyes pretreated with D.F.P. on the guinea-pig gut does not exclude the presence of a histamine mechanism, it appears at the present time more plausible to assume that the positive responses observed on tension and in a moderate degree on permeability of ciliary capillaries were brought about by one or another of the side actions of the drugs. The dilation of the pupils of normal rabbits would indicate the action of a sympathomimetic stimulus; however, antistine did not prevent full development of D.F.P. miosis but did influence the tension satisfactorily. The literature on antistine,[40–42] a drug which had been used effectively in allergic types of conjunctivitis,[43] does not give information on its anticholinergic activity.

The experiments with antihistaminic drugs (like those with calcium and adrenal cortex extract) should be considered preliminary. Benadryl and antistine could have exerted the beneficial influence on the ocular tension of the test lesion by mechanisms other than those operative on capillary permeability. The small difference in the protein level and permeation of the dye T-1824 between eyes treated with histamine antagonists and D.F.P. and eyes on which D.F.P. had been used alone might be explained by absorption of the former compounds from the conjunctiva of the treated eye in amounts sufficient to affect protein permeability of the ciliary capillaries in the other eye. The reduction of the protein level in the aqueous and of the staining intensity in ciliary processes of eyes treated with benadryl and antistine was relatively moderate. This differs greatly from the results of experiments with adrenergic drugs and with pituitrin. Further studies on this new group of drugs on the eye will be necessary for a better understanding of the observed action.

Summary

1. The rise in ocular tension following instillation of a 0.2-percent solution of di-isopropyl fluorophosphate in rabbits is apparently caused by increased permeability of the ciliary capillaries.

2. The outpouring of serum proteins into aqueous roughly paralleled the elevation of tension, but there were great discrepancies in individual experiments be-

tween height of tension and concentration of protein.

3. The blue Azo dye T-1824 was found useful in grading the capillaries of the limbus, iris, and ciliary processes for permeability to the dye and probably to serum albumin. The permeability of the ciliary capillaries greatly exceeded that of the capillaries of the limbus and iris under the influence of the same stimulus.

4. The diffusion of the dye from the circulating blood into the tissue interstices of the ciliary processes and the permeation into the iris and into the chambers of the anterior part of the eye were studied under the corneal microscope and histologically in sections of ciliary body and iris.

5. Biomicroscopical observations on the limbus vessels suggested that the capillaries dilated passively and simultaneously with the distention of the supplying arterioles and metarterioles caused by the cholinergic chemical mediator.

6. Adrenergic drugs and pituitrin effectively counteracted the action of D.F.P. on the ocular tension and capillary permeability in rabbits. The former diminished the miotic effect of D.F.P. far more than did pituitrin.

7. With the technique used, calcium gluconate and adrenal-cortex extract failed to influence the signs of increased permeability of the ciliary capillaries induced by D.F.P.

8. Benadryl, antistine, and to a minor degree pyribenzamine, prevented or reduced the elevation of intraocular pressure caused by D.F.P., but the action on capillary permeability was moderate. Only antistine did not weaken the miotic action of D.F.P.

We are indebted to Dr. M. I. Gregersen for supplying us with the dye T-1824, to Dr. B. W. Zweifach for valuable suggestions, and to Dr. A. Gellhorn for conducting the pharmacological tests with aqueous on the isolated guinea-pig gut.

We want to express our thanks to the the Research Division of Ciba Pharmaceutical Products, Inc., for the donation of the drugs pyribenzamine hydrochloride and antistine sulphate.

630 West 168th Street (32).

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TRANSFER OF ASCORBIC ACID AND RELATED COMPOUNDS ACROSS THE BLOOD-AQUEOUS BARRIER*

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The high concentration of ascorbic acid in the aqueous humor compared with that in the blood has been offered as presumptive evidence that this compound enters the aqueous humor as a result of a secretory process. Previous studies have shown that while this is true for adult animals the concentration of ascorbic acid in the aqueous humor in young animals is essentially the same as in the blood.[1] The difference in young animals has been explained by assuming that the blood-aqueous barrier is sufficiently permeable to permit rapid diffusion from the aqueous back into the blood.[2]

The implications inherent in the belief that the total transfer of ascorbic acid across the blood-aqueous barrier occurs as a result of a secretory process in adult animals, on the one hand, whereas, a predominant portion of the transfer occurs as a result of diffusion in young animals, on the other hand, have not been considered previously. Thus, if the transfer took place by secretion, it would be expected that the amount of ascorbic acid which could be transferred across the blood-aqueous barrier would be limited by some factor other than the quantity present in the blood; that is, that the secretory process is capable under ordinary conditions of handling but so much ascorbic acid. If the transfer occurs as a result of diffusion, it would be expected that there would be a direct relationship between the concentration in the aqueous and the blood irrespective of the concentration in the latter fluid. One of the objects of the present paper was to subject these inferences to experimental verification.

A second objective concerns the question of the specificity of the secretory process for compounds structurally like ascorbic acid. It is well known that other carbohydrates having similar size and solubility (namely, glucose) without exception are normally found to be present even in adult animals in the aqueous in lower concentration than in the blood. This is suggestive that any secretory process which can transfer ascorbic acid

* From the Howe Laboratory of Ophthalmology, Harvard Medical School. This work was supported in part by a grant from the John and Mary R. Markle Foundation. Read at the 16th scientific meeting of the American Association for Research in Ophthalmology, Inc., Atlantic City, June 10, 1947.

across the blood-aqueous barrier is relatively specific for this compound.

The question of the specificity of the transfer of ascorbic acid across the blood-aqueous barrier is of theoretical importance to a more complete understanding of the secretory process in general. Friedenwald and co-workers[3] have shown that ascorbic acid, presumably by reason of its ability to become reversibly oxidized and reduced, acts as a mediator in the oxidation-reduction system associated with the secretory process in general. It is not known, however, whether any portion of the molecule other than that concerned with oxidation reduction, that is, the enediol, is necessary either for secretion of other components of the aqueous humor or for the secretion of ascorbic acid itself. It would appear that this question could be resolved by studying the rate of transfer across the blood-aqueous barrier of the enantiomorph of ascorbic acid, d-isoascorbic acid, and d-glucoascorbic acid. D-isoascorbic acid differs structurally only in configuration and d-glucoascorbic acid in the addition of an extra CHOH group between carbon atoms 5 and 6 of ascorbic acid. Both compounds incidentally appear to have oxidation-reduction properties identical with ascorbic acid.

Materials and Methods

Albino rabbits were used for all of the experiments. The adult animals were fed a stock diet of Purina rabbit pellets, and the young animals were housed with their mothers.

The test substances were dissolved in glass-distilled water and injected intraperitoneally. Samples were taken from the eye at predetermined times under topical anesthesia (tetracaine HCl) using micropipettes as described previously,[1] and blood was removed by heart puncture. Upon collection, the samples were immediately placed in 4-percent metaphosphoric acid.

All of the analyses were done by means of the dichlorophenol-indophenol titration, and the results of all three compounds tested are reported in terms of ascorbic-acid equivalents. Since the method did not differentiate between the ascorbic acid normally present in the aqueous humor or blood and the compounds injected, the results must be interpreted in terms of change in concentration from the normal level. For the aqueous humor, the normal level is about 20 to 25 mg. percent; and for the blood, about 0.5 to 2.0 mg. percent.

Results

As to the manner in which ascorbic acid is transferred, Figure 1 shows that the concentration of ascorbic acid reaches a maximum in the blood within 20 minutes and that the concentration in the aqueous humor also increases to reach a maximum 60 minutes following intraperitoneal injection. Since the elevated level of ascorbic acid in the aqueous humor is maintained as long as the blood level remains constant, it may be assumed that a steady state is reached at this time.

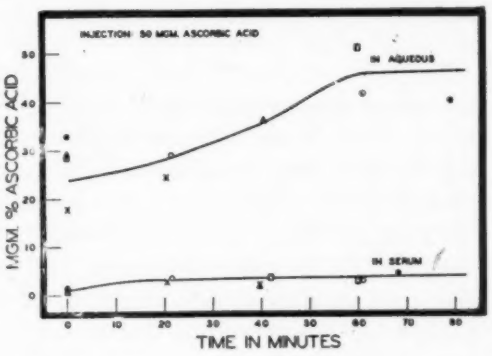

Fig. 1 (Kinsey). Shows the change in concentration of ascorbic acid in the serum and aqueous humor at various intervals following intraperitoneal injection.

Figure 2 shows the concentration of ascorbic acid in the aqueous 60 minutes after the injection of various quantities of this compound plotted as a function of the concentration in the blood. It is evident from the graph that the concentration in the aqueous increases rapidly with

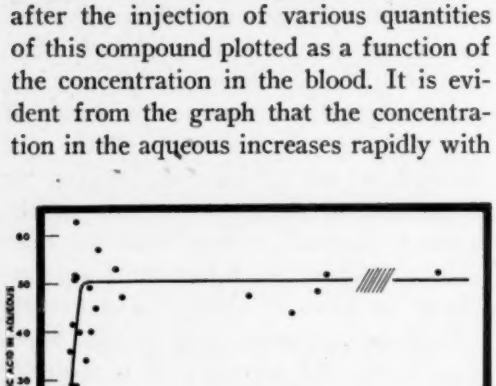

Fig. 2 (Kinsey). Shows the relative concentration of ascorbic acid in the aqueous humor and in the serum of adult rabbits.

increasing concentration in the serum until the level in the aqueous becomes 50 mg. percent. This occurs when the concentration in the serum is 3 mg. percent. With higher blood levels, no further increase in the quantity of ascorbic acid in the aqueous humor was observed, even though the concentration in the serum was elevated to 130 mg. percent.

The same experiments were repeated using young rabbits and the results are represented by the open circles in Figure 3. In this instance it will be seen that the concentration in the aqueous humor rises with increased concentration in the blood throughout the entire range. These results appear to be consistent with the hypothesis previously set forth; namely, that in adult animals ascorbic acid is transferred by secretory process, that some factor other than availability of this compound in the blood limits the amount which can be transferred across the blood-aqueous barrier, and that in young animals the transfer takes place primarily by the process of diffusion. That the blood-aqueous barrier in adult animals is impermeable to the simple diffusion of ascorbic acid is borne out by the observation that the concentration of ascorbic acid in the aqueous humor does not increase beyond 50 mg. percent, even though the blood level is more than double this concentration. It is interesting to note that molecules considerably larger than ascorbic acid—for example, sucrose—apparently can diffuse through the blood-aqueous barrier. The distinguishing characteristic between ascorbic acid and molecules like glucose and sucrose seems to be that, at the hydrogen-ion concentration found in the aqueous, ascorbic acid is charged; whereas, the sugars are not. This finding offers further support to the theory set forth by the author elsewhere[4] that electrolytes in general enter the eye by secretion; whereas, nonelectrolytes enter by diffusion.

With regard to the problem of the specificity of the secretory process, Figures 4 and 5 show the results of analyses made on serum and aqueous humor at various times after injecting d-iso ascorbic and

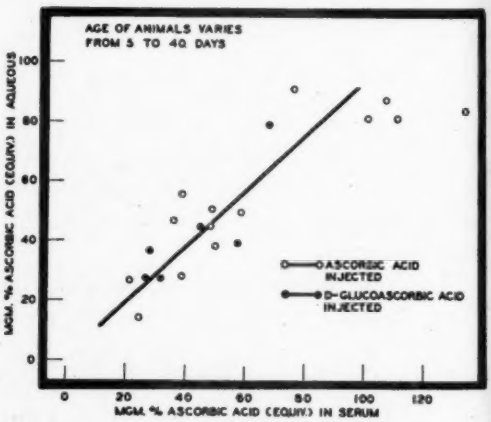

Fig. 3 (Kinsey). Shows the relative concentration of ascorbic acid (open circles) and d-gluco ascorbic acid (filled circles) in the aqueous humor and serum of young rabbits.

d-gluco ascorbic acid into adult rabbits. In both instances the concentration of material titratable with 2:6 dichlorophenol indophenol (expressed as mg. percent ascorbic-acid equivalent) increased in the serum, but only in the case of d-iso ascorbic acid did the concentration of the injected material rise in the aqueous humor.

The filled circles of Figure 3 show the

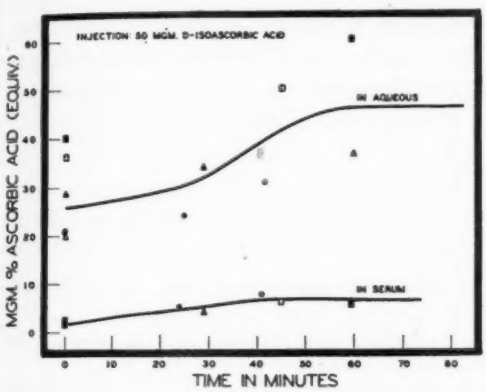

Fig. 4 (Kinsey). Shows the change in concentration of d-iso ascorbic acid in the serum and aqueous humor at various intervals following intraperitoneal injection.

concentration of d-gluco ascorbic acid in the serum and aqueous humor of young rabbits. Unlike the results obtained in the adult animals, it will be seen that d-glucoascorbic acid enters the aqueous humor of young animals and does so in proportion to the concentration in the serum.

The results indicate that the secretory process is apparently selective for ascorbic acid or its optical isomere and are suggestive that ascorbic acid forms an integral part of the secretory mechanism as proposed by Friedenwald.[3] The secretory process is not as specifically dependent upon a particular structure, however, as are the mechanisms whose malfunction results in scurvy, since d-isoascorbic and d-glucoascorbic have but 1/10 and 1/100 antiscorbutic power of ascorbic acid, respectively.

From the point of view of chemical mechanism, it may be inferred that in addition to the possible participation of that portion of the molecule responsible for the oxidation-reduction property; that is, the enol groups, the part of the molecule around carbon-atoms 5 and 6 are also necessary to the secretory process.

Summary

The distribution of ascorbic acid in the aqueous humor and blood of adult and young rabbits was determined under steady-state conditions. In adult animals the concentration of ascorbic acid in the aqueous was found to increase rapidly with increasing concentration in the blood until the concentration in the aqueous reached 50 mg. percent. This occurred with a serum concentration of approximately 3 mg. percent. With higher blood levels no further increase occurred in the concentration of ascorbic acid in the aqueous even though the concentration in the bloood was more than double that in the aqueous humor.

In young animals the concentration of ascorbic acid in the aqueous was found to vary directly with the concentration in the blood. These differences in distribution

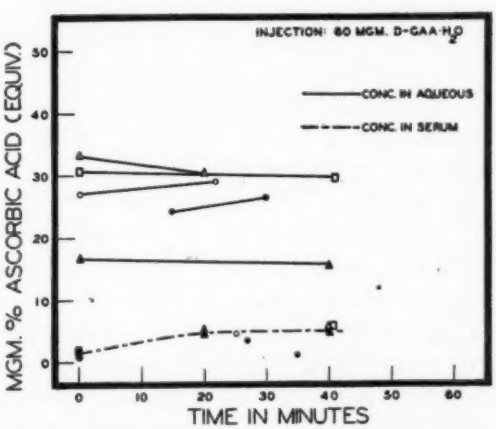

Fig. 5 (Kinsey). Shows the change in concentration of d-gluco ascorbic acid in the serum and aqueous humor at various intervals following intraperitoneal injection.

were thought to indicate that ascorbic acid enters the aqueous humor as a result of a secretory process in adult rabbits; whereas, in young animals the predominating factor in determining the distribution ratio is diffusion. Furthermore, they show that in adult animals some factor, other than availability of this compound in the blood, limits the amount which can be secreted across the blood-aqueous barrier.

The specificity of the secretory process for compounds structurally like ascorbic acid was investigated by injecting d-iso and d-gluco ascorbic acid into the peritoneal cavity and determining the rate of entrance of these compounds into the aqueous humor in adult and young rabbits. It was found that d-iso ascorbic acid entered the aqueous but no transfer of d-gluco took place across the blood-aqueous barrier in adult animals. These results indicate that the secretory process is apparently selective for ascorbic acid or its optical isomere (d-isoascorbic acid). The selectivity appears to be unrelated to the antiscorbutic action of these compounds. No selective transfer was observed for these compounds in eyes of young animals.

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A STATISTICAL STUDY OF GLAUCOMA*

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In the introductory surveys of glaucoma in monographs and textbooks, there are many statistical data which are, to a certain extent, copied from one work to another. However, it is not always easy to gain a clear impression of the conditions mentioned; such as, the frequency of glaucoma, its distribution according to sex, errors of refraction, and so forth. For many of the conclusions quoted belie each other, often to the confusion of the reader. This may be so not only because the figures are often comparatively small, but also because they hail from material which is so ill-assorted that they are not forthwith comparable.

To a certain extent this fact can be traced to the neglect of some writers to distinguish between the various forms of glaucoma. To be sure, secondary glaucomas are, as a rule, kept by themselves, and this is usually the case also with glaucoma infantum and, perhaps, glaucoma juvenile. Glaucoma simplex and congestive glaucoma are, however, often lumped together. Hence the difficulty in comparing data from different countries. Most statistics show wide fluctuations in the relationship between glaucoma simplex and congestive glaucoma, the one being dominant in certain areas, the other elsewhere. At any rate, it would seem that congestive glaucoma is particularly common in southern countries, certainly more common than in the North where glaucoma simplex is by far the more common form.

My object in presenting certain figures illustrative of conditions in Norway, compared with data I have obtained elsewhere, is not primarily to contribute a new name or new figures to the long series of earlier statistics. I believe that my Norwegian data may prove deserving of notice and may, perhaps, help to clarify certain problems because they are large in comparison with the figures presented by many other investigators. Besides, my data are so uniform that they should reflect with considerable accuracy the conditions with which we are dealing. As with all statistics, however, the numerical results must be treated critically if we are to avoid drawing false conclusions from them. I would therefore make certain reservations with regard to some of my figures.

SEX INCIDENCE OF GLAUCOMA

My material is derived from the University Eye Clinic in Oslo, and it belongs to the period, 1920 to 1939. During these 20 years, 24,127 patients were admitted to the Eye Department, 13,334 men and 10,793 women. The ratio of men to women was 55.3 to 44.7 percent.

This apparent preponderence of men patients does not make it at once permissible to conclude that eye diseases serious enough to require hospital treatment are more frequent in men than in women in Norway. In the first place, the University Eye Clinic has always had more beds for men than for women. This condition reflects the experience that there really is greater need for beds for men. The capacity of the Eye Department has always, right up to the abnormal conditions during the war, been so great that it has, on the whole, been able to accept all the patients for whom applications for admission have been made. The difference in the numbers of beds available for men and women has, therefore, had scarcely

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any influence on the relative number of men and women patients admitted.

Another factor to be taken into account concerns the patients whose eye diseases may require hospital treatment, but who remain at home and to some extent at work. For various reasons they do not seek medical advice, or they beg to be excused, or they flatly refuse admission to hospital. It is probable that most such patients are women. For, once a man is so ill that he must remain at home, away from his work, it is seldom difficult to persuade him to go into a hospital. As a rule, a woman must be much embarrassed by eye disease before she completely abandons work at home. Instead of submitting to complete idleness in a hospital, she often remains ailing at home. I consider, therefore, that the figures, 13,334 for men and 10,793 for women, correctly express the relative need of the two sexes for hospital beds for eye disease. However, I doubt if they reflect the true frequency of serious eye disease in the community.

Incidence in literature

What of the incidence of glaucoma in the two sexes? The information on this score which I have found in the literature has given me no clear picture.

In *Nordisk Lärebok i Oft.* (1936) we read that: "the predisposition is much the same for both sexes, but it is perhaps somewhat greater for women, particularly in the case of acute glaucoma." *Kurzes Handbuch* (1931) quotes Priestley Smith, according to whom women are in the majority in the ratio of 6 to 5. Schmidt-Rimpler is quoted as putting this ratio at 5 to 4. Lugue states that 207 of 300 patients were women. In Beren's *The Eye and Its Diseases* (1936) it is stated that the condition is found somewhat more frequently in women than in men in about the ratio of 6 to 4. In *Traité d'Ophtalmologie* (1938), Morax is quoted as saying that most authorities believe that chronic glaucoma is about equally common in the two sexes.

In his book on glaucoma (Graefe-Saemisch, 1933), Peters quotes several statistics including those of Schmidt-Rimpler, but he also writes that, according to other authorities, men are more susceptible than women to this disease. He does not, however, give any figures. He goes on to say that Neuffer in Tübigen finds women patients in the majority. He also refers to two writers who have come to conflicting conclusions. Rohner (Basel, 1927) believes that there is no difference between the sexes up to the age of 65 years, after which women are in the majority (396 cases). Luge (1929), on the other hand, found women in the majority, particularly after the menopause. In higher age groups, however, the glaucoma rate was again highest in men!

Elliot (1922) also quotes several of the above-mentioned writers as well as Kogashima, who found glaucoma more frequent in women than in men in the ratio of 62 to 38 percent. Elliot says, however, that in the chronic, noninflammatory forms, the incidence in men may, perhaps, be greater by a small margin.

It will thus be seem that the literature gives us an exceedingly nebulous picture with regard to the sex incidence of glaucoma. This confusion arises from the fact that many writers do not distinguish in their statistics between glaucoma simplex and congestive glaucoma. All who have kept the two conditions separate agree that congestive glaucoma at any rate affects women more often than men.

Incidence in Norway

How do matters stand here in Norway? Taking glaucoma simplex first, I note that it was diagnosed in 2,024 of the 24,127 patients admitted to the eye clinic; that is, in almost 8.4 percent. Of these 2,024 patients, 1,261 (62.3 percent) were

men and 763 (37.7 percent) were women. These figures come from the annual reports of the department. Among them there may be a certain number of patients admitted to the department on several occasions for treatment of the other eye, for reoperation, and the like. On each occasion they received a new case record number and were thus counted as new patients each time. To ascertain if this duplication is of any importance, I have made a direct count of 1,012 patients, and have found 637 of them to be men and 375 women—figures in exact conformity with those of the annual reports. The men were so much in the majority that it cannot simply be due to the greater number of beds for them.

We should also note that glaucoma patients were never refused admission to the department. To be sure, applications on behalf of glaucoma patients for admission are sometimes made under other diagnoses, but this source of error can hardly have played any important part, since we may safely assume that any mistaken diagnoses were equally distributed between the two sexes. It is my conviction, therefore, that the 1,261 cases of glaucoma simplex among men and the 763 cases among women give us an approximately correct impression concerning the distribution of glaucoma simplex between the two sexes in Norway.

The larger number of men becomes further emphasized when we recall that women are in the majority in the age groups in which glaucoma occurs. According to official Norwegian statistics, the census of 1930 showed that, over the age of 50 years, the ratio of men to women was 45.5 to 54.5 percent.

Of 142 patients with bilateral glaucoma, with absolute glaucoma in one eye, there were 96 men and 46 women, and among 118 patients with ***nearly*** absolute glaucoma of the worse eye, with vision of light perception only or finger counting under 2 meters, there were 82 men and 36 women. Thus, among a total of 260 patients with absolute or nearly absolute glaucoma of the worse eye, there were 178 men (68 percent) and 82 women (32 percent). These figures tally very well with the ratio of men to women in the entire study.

When we consider the cases of congestive glaucoma, we find another state of affairs. Of the total of 143 patients treated for this condition in the Eye Clinic in the period 1920 to 1939, 51 were men and 92 were women, a ratio of 36 percent to 64 percent. In other words, we have here almost the opposite of what we found in glaucoma simplex. However, one of the few points on which all writers agree is that women are more subject to congestive glaucoma than men.

The various statistics show great discrepancies with regard to the relative frequency of glaucoma simplex and congestive glaucoma. This is so to some extent because of an uncertain nomenclature. The usual classification is as follows:

1. Acute congestive glaucoma or merely acute glaucoma.
2. Chronic congestive glaucoma.
3. Chronic glaucoma simplex or merely glaucoma simplex. (Sometimes we find a special group.)
4. Absolute glaucoma.

The term applied to the first group is clear and cannot be misunderstood. As a rule, the diagnosis is not difficult, at any rate not if it is possible to examine the patient and to obtain a case history with its record of typical attacks. The shallow anterior chamber and the lack of exfoliation are also guides to the diagnosis.

Chronic congestive glaucoma, the term applied to the second group, expresses a

vague conception. It may include genuinely acute forms which lack the usual stormy course of an attack. It usually covers those cases of glaucoma simplex which have begun insidiously, which have gradually developed an ever-increasing pressure, and which have finally presented more or less marked manifestations of chronic congestion and inflammatory phenomena. The English term "chronic incompensated glaucoma" gives a correct picture of this condition without taking the onset of the disease into consideration. Presumably certain cases of secondary glaucoma, notably when they follow thrombosis of the central vein, will also be included in this group.

Group 3 includes those cases we are accustomed to describe merely as glaucoma simplex, and this designation is, as a rule, clear and straightforward.

The term applied to Group 4, absolute glaucoma, is an unfortunate one, for it merely signifies a stage in the development of the disease and does not tell us the form of glaucoma with which we are confronted. I believe that the cases usually included under the diagnosis of absolute glaucoma represent, in most instances, glaucoma simplex in a far advanced stage but without manifestations of irritation. When there are signs of irritation, the diagnosis is often chronic congestive glaucoma. The cases of acute glaucoma leading to blindness are, as a rule, easily recognized and are accordingly given the diagnosis of acute glaucoma.

In his statistical analysis, Ahlström gives the frequency of the various forms of glaucoma as follows:

Classification	*Percent*
1. Prodromal conditions in	3.6
2. Acute glaucoma	6.5
3. Chronic congestive glaucoma	24.9
4. Glaucoma simplex	41.7
5. Absolute glaucoma	23.3

The terms employed for the first and last groups are primarily indicative of stages of the disease; whereas, the terms in the three other groups refer to the clinical manifestations of the disease. The groups cannot, therefore, be compared with each other without further delineation.

A classification resembling Ahlström's is adopted by v. Grosz of Budapest in his large statistical study, extending over 30 years, of 52,032 patients, 5,958 of whom (11.4 percent) suffered from glaucoma. He presented the following groups:

Classification	*Number*	*Percent*
1. Glaucoma inflammatorium in a prodromal stage.	453	7.8
2. Glaucoma inflammatorium acutum.	792	13.3
3. Glaucoma inflammatorium chronicum	2,967	49.7
4. Glaucoma absolutum.	1,124	18.8
5. Glaucoma simplex.	622	10.4

In this classification Groups 1 and 2 can be fused together. Group 3 evidently belongs, in the main, to Group 5, as does Group 4. By limiting ourselves to two groups we shall, at any rate, not include too many cases in the glaucoma inflammatorium acutum group.

These statistics show that the relationship of glaucoma inflammatorium to glaucoma simplex varies greatly. While, according to Ahlström, glaucoma acutum is responsible for 6.5 percent (at most 10.1 percent) of all the cases of glaucoma, the corresponding figures, according to v. Grosz, are 13.3 percent (or at the most 21.1 percent).

In his *The Eye and Its Diseases,* Berens says that glaucoma simplex is about 10 times as common as the incompensated forms of glaucoma, but in a later table he quotes figures from his own practice showing 77 cases of compensated, 33 acute incompensated, and 44 chronic incompensated.

My own statistics show: Glaucoma inflammatorium, 143 cases of 6.6 percent; glaucoma simplex, 2,024 cases or 93.4 percent. These figures tally quite well with Ahlström's, and this would be expected since the ethnical background of Ahlström's patients and mine is similar; whereas, v. Grosz's patients come from southern and eastern countries and belong to other ethnical groups.

Refractive errors in glaucoma

What are the most common refraction findings in patients who develop glaucoma? Much information is available on this, but the various textbooks deal, to a large extent, with statistics from the same authors, and figures are either not mentioned or are comparatively small.

A statement in *Nordisk Lärebok* says: "... among refraction findings hyperopia seems to predispose to stasis glaucoma. Simple glaucoma appears to occur independently of the state of refraction of the eye."

According to a statement in *Traité d'Ophtalmologie,* Gilbert in Munich found hypermetropia in 38 percent of his cases and emmetropia or myopia in 62 percent (71 cases), but hypermetropia was found in 77 percent of the cases of glaucoma acutum. Morax insists that inverse astigmatism is of some importance, and he recommends pressure control when this error of refraction is found.

Elliot says: "Hyperopia is the commonest refraction error met with in eyes affected with primary glaucoma." He quotes Gilbert and also Lange, who found myopia in 43 percent of his cases. According to *Kurzes Handbuch,* hypermetropic eyes are quite definitely more often attacked by glaucoma that myopic eyes. Peters remarks that hypermetropia is said to have a causal relationship to glaucoma because of the smallness of the cornea, the narrower filtration angle, and the greater rigidity of the sclera. But myopia also occurs frequently (cit. Lange and Gilbert).

In his textbook, Berens says: "The refractive error of the eye is of interest, as it was formerly believed that only hyperopic eyes were subject to compensated glaucoma. We now know that this view is erroneous and that, although the anatomic build of the hyperopic eye renders it more susceptible to glaucoma than that of the myopic eye, other factors are of greater importance."

He then proceeds to relate his own experience with his last 188 cases of glaucoma, only 77 of which were "compensated." Among these 77 cases were 50 of hyperopia (65 percent), 19 were cases of myopia (25 percent), and 8 showed mixed astigmatism (10 percent). Thus, strangely enough, he had no case of emmetropia. Among his cases of hyperopia there were 24 with less than +1.50D. of hyperopia, and among his cases of myopia there were 15 with less than 6.00D. of myopia.

In the opinion of certain writers, however, the development of glaucoma in persons with myopia is so rare as to inspire the publishing of several cases in which special reference is made to the combination of the two conditions. In 1929, Schenk stated that glaucoma seldom occurs in myopics; whereas, in the same year Meyerhofer stated that glaucoma and myopia often occur together in Egypt (in 12 out of 183 cases).

For my own part, I have kept a record of the refractive errors in glaucoma only during the 11 years, 1928 to 1939. The refraction was in every case measured before operation by Donders' subjective method. During this period, refraction conditions of 1,417 eyes suffering from glaucoma simplex were recorded. The refraction conditions were as follows:

Type	*Percent*
Hyperopia	25.6
Emmetropia	50.7
Myopia	19.1
Astigmatism	4.6

I have also divided up these cases into smaller groups so as to show the occurrence of the more marked errors of refraction (table 1).

Table 1 shows that most of the cases group themselves about emmetropia in about 30 percent of these cases; hypermetropia in about 55 percent; and myopia in about 15 percent. A refraction of +1.00D. is counted as hypermetropia. If his curve is correct, my figures do not show that persons with hypermetropia are particularly subject to glaucoma simplex, but rather the reverse; that is, that they are less likely to contract glaucoma than persons with other refractive errors. To facilitate a comparison, I have placed Herrnheiser's figures for refraction con-

TABLE 1

REFRACTIVE CONDITIONS IN GLAUCOMA SIMPLEX

Refractive Error	More Than +2. D.	Less Than +2. D.	Between +.5 D. −.5 D.	Less Than −2. D.	Less Than −6. D.	More Than −6. D.	Astigmatism +	Astigmatism −	Astigmatism Inverse
Number of Patients	79	288	719	178	78	23	23	18	29
Percent	5.5	20.1	50.7	12	5.4	1.6	1.6	1.2	2.0

which is the dominant refraction condition in glaucomatous eyes. The exaggerated errors of refraction are represented by small groups. It is particularly striking that the hypermetropic group is so small.

What is the frequency of the various errors of refraction in a normal group? Many investigations have been undertaken of refraction conditions in different groups of the community and also in certain age groups, but I have not found any investigation giving a straightforward account of the various refraction conditions in the higher age groups. However, Herrnheiser (*Kurzes Handbuch*) has presented a curve showing the distribution of refraction conditions in various age groups. After the age of 30 years, conditions are more or less constant, but with a tendency to an approach to emmetropia after the age of 70 years in the subjects of both myopia and emmetropia. He says that emmetropia occurs

ditions in normal groups beside my figures for these conditions in glaucoma groups.

Normal (Herrnheiser)	*Glaucoma* (Holst)
Hypermetropia, 55.0%	Hypermetropia, 25.6%
Emmetropia, 30.0%	Emmetropia, 50.7%
Myopia, 15.0%	Myopia, 19.0%

Here it is remarkable that the incidence of myopia is higher among glaucoma patients than in a normal group; whereas, hypermetropia is only half as frequent among glaucoma patients as in a normal community.

It is conceivable that my figures are vitiated by several sources of error. As already pointed out, the refraction was measured before operation, but patients in several cases had suffered from glaucoma for some time and had, as a rule, been treated with pilocarpine. Although we were dealing with elderly patients, some of them could have retained a little

accommodation. It such cases, pilocarpine may have induced an "accommodation cramp" which can simulate myopia. Further, it is possible that, in some cases, the glaucoma may have led to degenerative changes in the eye, such as early cataract, which betrayed themselves as a lenticular myopia. My material does not provide sufficient information to determine whether many of my patients have become myopic as the result of pilocarpine medication or through the progression of the glaucoma, but the shifting of the refractive conditions from hypermetropia to emmetropia and myopia could have glaucoma as a causal or predisposing factor. Nor can any definite answer to this question be obtained by investigating the refractions of patients with unilateral glaucoma and anisometropia.

In 80 of 97 cases of unilateral glaucoma and anisometropia, the refraction showed the glaucomatous eye to be more myopic than that of the healthy eye, but, as already pointed out, we do not know what the refraction of the glaucomatous eye was *before* the manifestation of signs of glaucoma.

It will be noted (table 1) that I found astigmatism in 4.8 percent of the cases studied (myopic, regular astigmatism a little more frequently than hypermetropic, regular astigmatism). The fact that as great a proportion as 2 percent of my cases showed inverse astigmatism seems to support Morax's assumption that this condition predisposes to glaucoma. We should, therefore, do well to follow his advice and carefully supervise the ocular pressure of patients suffering from inverse astigmatism.

Unfortunately, with regard to congestive glaucoma, I have information concerning the refractions of only 59 patients with a total of 75 eyes presenting this condition. Their refractions are shown in Table 2. The figures in Table 2 do not differ greatly from Herrnheiser's normal figures. If we are to draw any conclusion whatever from this small number of cases, it would seem that hypermetropia plays a considerably more important part in congestive glaucoma than in glaucoma simplex, while the combination of myopia and congestive glaucoma is more rare than that of myopia and glaucoma simplex.

TABLE 2

REFRACTIVE CONDITIONS IN CONGESTIVE GLAUCOMA

	Hypermetropia			Emmetropia	Myopia		Unknown
Refractive Error	More Than +6.00 D.	More Than +2.00 D.	Less Than +2.00 D.		Less Than −6.00 D.	More Than −6.00 D.	
Number of Eyes	3	11	19	25	6	2	9
Total (75 Eyes)	33			25	8		9

FIRST EYE TO BE ATTACKED

Which eye is most frequently the first to be attacked by glaucoma? According to Schmidt-Rimpler, the right eye is not only more often the first to be involved but also, when the disease is confined to one eye, the right is most often that one eye.

When the patient presents himself with advanced bilateral glaucoma, it is not

always easy, however, to say which was the first eye to be attacked. Frequently, he notices definite signs of the disease in one eye before the other, and the development of glaucoma is often marked by such different stages in the two eyes that we are justified in concluding that it began in the eye in which the disease is most advanced. A record of 1,040 patients kept by me during the last 11 years shows that glaucoma began in the right eye in 390 cases, and in the left eye in 486 cases; whereas, in 164 cases information on this point was lacking for various reasons. These figures do not tally with those given by Schmidt-Rimpler, but they do agree with the records of the University Eye Clinic in Oslo for the period 1928 to 1939 when a greater number of left eyes (375) than right eyes (345) were operated for glaucoma simplex. The small difference between these two figures *may*, to a certain extent, be explained by this hypothesis:

If it is true that glaucoma more frequently attacks the left eye before it does the right eye, *then* more left than right eyes are the seat of absolute glaucoma and are *not* operated because the condition in the left eye is hopeless; whereas, the right eye, still possessing useful vision, is operated on.

This hypothesis can, moreover, be substantiated by facts. Of 189 eyes presenting absolute glaucoma, or nearly absolute, and not subjected to any glaucoma operation, 102 were left eyes and 87 were right eyes. Further, among 196 patients with unilateral glaucoma, the left eye was involved in 119 cases, the right eye in 77. These figures would seem to indicate that the left eye is more prone to glaucoma than the right, but why this is so I cannot say.

Exfoliation of lens capsule

The presence or absence of exfoliation of the lens capsule is of great interest in cases of glaucoma. Here in Norway, Hörven's researches in this field have attracted special attention. He says that "we can take it as proved that between 60 and 70 percent of the patients presenting exfoliation suffer at the same time from glaucoma." Indeed, Vogt has found glaucoma in as great a proportion as 75 percent of his cases of exfoliation. Several other writers mention similiar figures.

How many glaucoma patients suffer from exfoliation? Data concerning this point are most varied. According to Hörven, various writers put this rate at 8 to 9 percent (Vogt, Blaickner) while others put it at 40 to 50 percent (Malling, Baumgart, Lindberg). Hörven, himself, found that 85 percent of his 150 glaucoma patients suffered from exfoliation. However, it is surprising how little interest has been taken in this matter and how seldom exfoliation is demonstrated. In certain hospitals the lists of diagnoses include a special heading, "glaucoma capsulare," under which very modest figures are to be found.

In my study, examinations for exfoliation have been carried out only since 1936 (after the appearance of Hörven's thesis for the degree of Doctor of Medicine). During this period information about exfoliation has been obtained in the study of 459 cases of glaucoma. It was found in 375 cases (82 percent). This observation falls well in line with Hörven's. All the patients were examined in focal illumination with Hartnack's loupe. Most of the patients, who yielded negative findings on this examination, were also examined more closely with a slit-lamp; some, but not all, under glaucosan mydriasis. It is conceivable that a more consistent and detailed examination would have shown still more cases of exfoliation.

It is noteworthy that among these 459

patients, there were 53 with unilateral glaucoma in whom exfoliation was found in one eye only, and that one eye was invariably the glaucomatous eye. We are, therefore, fully justified in assuming a close association between exfoliation of the lens capsule and the condition we call glaucoma simplex.

Unfortunately, my statistics regarding any association existing between congestive glaucoma and exfoliation are most incomplete. In only 10 cases was an examination for exfoliation recorded. In none of these 10 cases was exfoliation demonstrated.

Summary

At the University Eye Clinic in Oslo, in the period 1920 to 1939, there were 24,127 admissions, 13,334 patients (55.3 percent) were men, and 10,793 (44.7 percent) were women. Among these 24,127 admissions were 2,024 cases (8.4 percent) of glaucoma simplex; 1,261 were men (62.3 percent), and 763 women (37.7 percent). The fact that men greatly outnumbered women is more surprising when it is remembered that in the age group (over 50 years) in which the incidence of glaucoma is most high, the percentage of men to women is 45.5 to 54.5.

Of the 143 patients suffering from congestive glaucoma, 36 percent were men, 64 percent, women; that is, a ratio almost the reverse of that for glaucoma simplex.

A comparison of the frequency of the two forms of glaucoma shows that glaucoma simplex constituted 93.4 percent of all the cases; whereas congestive glaucoma constituted only 6.6 percent.

With regard to the refractions of patients with glaucoma simplex, hypermetropia was found in fully 25 percent; emmetropia in fully 50 percent; and myopia in 19 percent; and almost 5 percent were astigmatic. These figures, when compared with Herrnheiser's "normal curve" show that, in the present material, there were only half as many subjects of hypermetropia as one can expect to find in a normal population; that there were more cases of myopia; and that the preponderance of emmetropia was very marked.

The information provided by the present study fails to show whether the shifting of refraction in the direction of myopia is a predisposing cause of glaucoma, or a consequence of it, or the result of treatment given for it (changes in the lens, pilocarpine).

Inverse astigmatism was found in as great a proportion as 2 percent.

Among 1,040 glaucoma patients, there were 390 whose disease began first in the right eye, and 486 whose disease began first in the left eye; whereas, in the remaining 164 cases information was not forthcoming as to which eye was first attacked.

In 459 cases an examination was undertaken for exfoliation of the lens capsule which was found in 375 cases (82 percent).

In the 53 cases of unilateral glaucoma in which exfoliation was found on only one side, it was always found in the glaucomatous eye only. The reverse condition, with exfoliation in the healthy eye, but not in the glaucomatous eye, was never observed.

Pilestredet 28.

THE DIAGNOSIS OF EARLY GLAUCOMA*

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In the presence of symptoms of unrelieved asthenopia, subnormal or unequal accommodation, a variation of more than a few mm. in the tension of the two eyes, sclerosis of the lens nucleus, or the history of glaucoma in the family, one should institute a searching examination for evidence of early glaucoma. Contraction of the peripheral fields and cupping of the optic nerve are late symptoms. Although routine determination of the ocular tension may be found to be normal, enlargement of the blindspot is present if the tension has been recently elevated. At this early stage, when paracentral field changes are present, the process may still be a reversible one, but normally does not occur until the tension has been normal for a considerable period of time. Since in early glaucoma the tension may be elevated for only a few hours each day, enlargement of the blindspot is found in the presence of normal daytime tension. The evaluation of the changes from the normal to the enlarged blindspot, the reversibility of the enlargement, along with the details of the study are here described.

METHODS FOR DIAGNOSIS

Many methods for the diagnosis of early glaucoma have been described, especially methods of increasing the intraocular pressure. In such instances the diagnosis is made upon the increased pressure alone. These methods are: massage test, Knapp, 1912; dark-room test, Seidel, 1914; decubitus test, Köllner, 1916; adrenalin test, Knapp, 1921; fluorescein, Thiel, 1922; caffeine test, Wegner, 1925; drinking test, Schmidt, 1928; venous-congestion test, Wegner, 1930; paracentesis test, Kronfeld, 1930; reading test, Gradle, 1931; mydriasis test.

Ferree, Rand, and Sloan have shown the sensitivity of the paracentral area to scotomas and the value of red and green test objects in individuals suffering from frank glaucoma with constantly elevated tension (sometimes controlled with miotics).

Sloan described the early paracentral field changes in early glaucoma, principally arcuate or sickle type of scotomas. These were divided into (1) scotomas which encircled the fixation point, (2) relative scotomas present without absolute scotomas, (3) scotomas which decreased or disappeared with the use of pilocarpine. Sloan further confirmed the opinion of Samojloff that the sickle type of scotoma disappears quickly after the use of pilocarpine but only after prolonged use in more advanced cases.

Sloan, Peter, and Traquair have discussed the association of the arcuate scotoma with the blindspot, and its isolation from the blindspot. On the other hand, Thomasson found that an isolated scotoma is never an early manifestation of glaucoma, all early scotoma being attached to the blindspot itself.

This paper presents data on 27 cases of increased intraocular pressure without evidence of cupping of the optic nerve or changes in the peripheral field, one case of slight cupping, two cases of shallow anterior chambers, and three cases without increased tension. These patients, observed over a period of 6 months to 7½ years, have had frequent

* Read at the 82nd annual meeting of the American Ophthalmological Society, San Francisco, California, June, 1946.

determinations of the ocular tension plus detailed study of the blindspots. Every case of glaucoma with cupping has been eliminated except the one case previously mentioned.

Tonometric readings

In the diagnosis of early glaucoma there seem to be several difficulties in taking tonometric readings. It is not easy to teach residents and ophthalmic assistants the art of taking tonometric readings, so wide variations occur. Slight variations of 3 to 5 mm. cause marked changes in the paracentral field; whereas, it may be difficult to make a diagnosis of glaucoma on a rise of from 3 to 5 mm. of intraocular pressure. Evans has stated that careful mapping of scotomas is a much more sensitive indication of increased intraocular pressure than any tonometric measurement. It is believed also that residents and assistants obtain more uniform field studies than tonometric readings, and that both are essential in establishing a diagnosis of glaucoma.

Many reasons besides routine tonometric readings were present in this group for detailed field studies. Rapidly progressive presbyopia, unequal accommodation, asthenopia not relieved by adequate correction, difficulty in reading in the early morning, the presence of nuclear sclerosis, and blindness in the mothers of three of the patients were some of the reasons for study.

The tonometer used was of the Gradle-Schiøtz type. It was sent to a standardizing station and found to be in good mechanical order. Reconversion tables were never received and the tonometer was standardized as follows: Many routine tests were performed on the blindspot with tensions varying from 20 mm. upward. It was found that no change occurred in the blindspot with a 1-mm. test object on the tangent screen at one meter with tensions up to and including 28 mm., with three exceptions noted. Similar normals were present for 4-, 8-, and 12-mm. red test objects at one meter. When, however, the tension was above 28 mm., demonstrable changes were present in the paracentral field. I have observed also that all individuals seemed to have the same limit of normal tension.

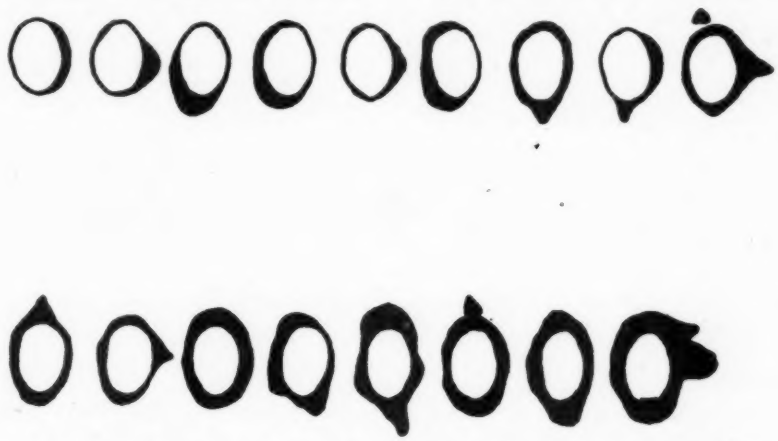

Fig. 1 (Grant). Changes in blindspot in early glaucoma as shown in several cases without cupping of the optic nerve but having increased tension.

Enlargement of blindspot

The earliest change noted is a relative

enlargement of the blindspot which may be observed for red test objects of 4, 8, and 12 mm. The earliest absolute changes are winglike scotomas which appear on the temporal sides of the blindspot either

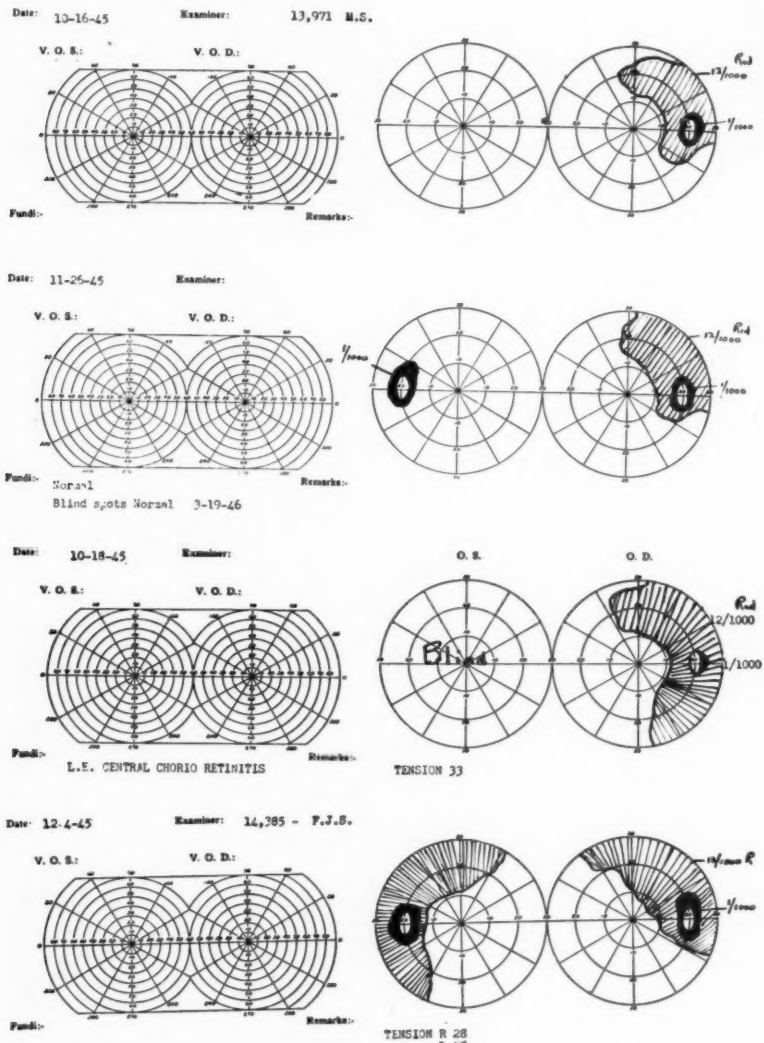

Fig. 2, Part 1 (Grant). Changes in blindspot for 1½ mm. white and 12 mm. red on a standard 1-mm. screen.

as tonguelike protuberances or as a gentle elongated enlargement along the whole side. The upper and lower poles remain normal and may have a very pointed appearance if there is marked widening, or the blindspot may be almost round. At the onset these scotomas appear and disappear with the rise and fall of tension, in some cases disappearing completely if the tension falls to normal and remains so. Improvement, however, occurs very slowly, and several weeks or months may elapse before normalcy is reached. Small tonguelike elongations appear at the upper and lower poles only after lateral enlargement

has occurred. It would appear that the coalescence of these small winglike and tonguelike scotomas ultimately causes the permanent irregular enlargement of the blindspot. No sickle or arcuate type of scotomas appears attached to or free from the normal blindspot, only on the enlarged blindspot. In the early or late stages, the sickle type is separated from the blindspot by a small area of vision, especially so if these appear for an hour or so when the tension is elevated, and disappear with the reduction of tension. Only when the condition is more advanced is the arcuate scotoma attached to the blindspot itself. These observations concur with those of Thomasson.

These early changes are easily demonstrated in individuals who have normal tension for most of the day with elevation for only a few hours in the early morning, or elevated artificially by one of the previously suggested methods. I have found, however, that checking of the tension and blindspots very early in the morning as soon as the patient is out of bed will, in most instances, eliminate the necessity for artificial elevation of the tension.

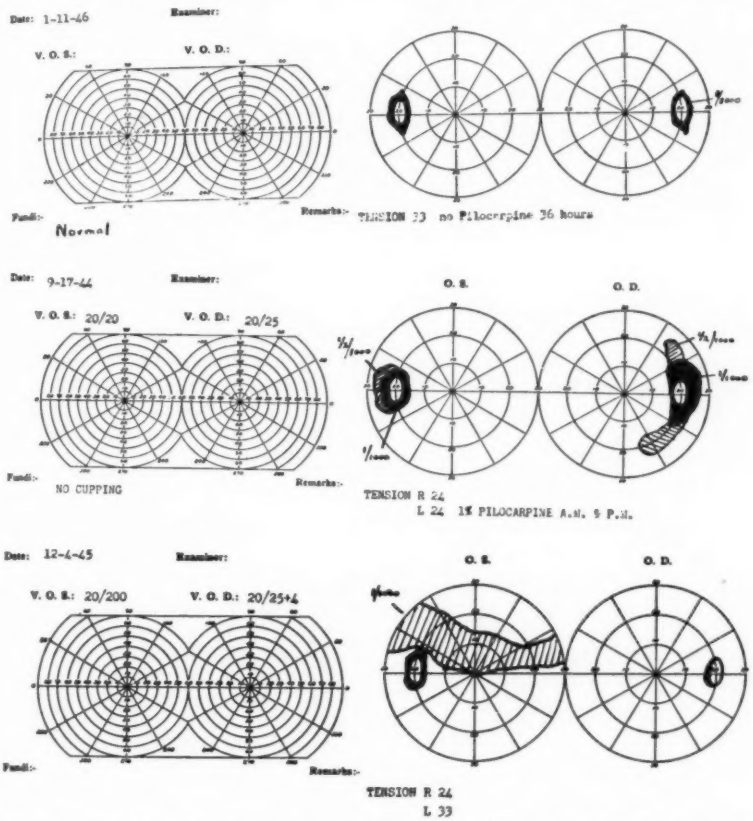

Fig. 2, Part 2 (Grant). Changes in blindspot for 1½ mm. white and 12 mm. red on standard 1-mm. screen.

Case reports

Mydriasis test

The mydriasis test produces alarming changes in the blindspot in one hour, when positive, as is illustrated by the following cases:

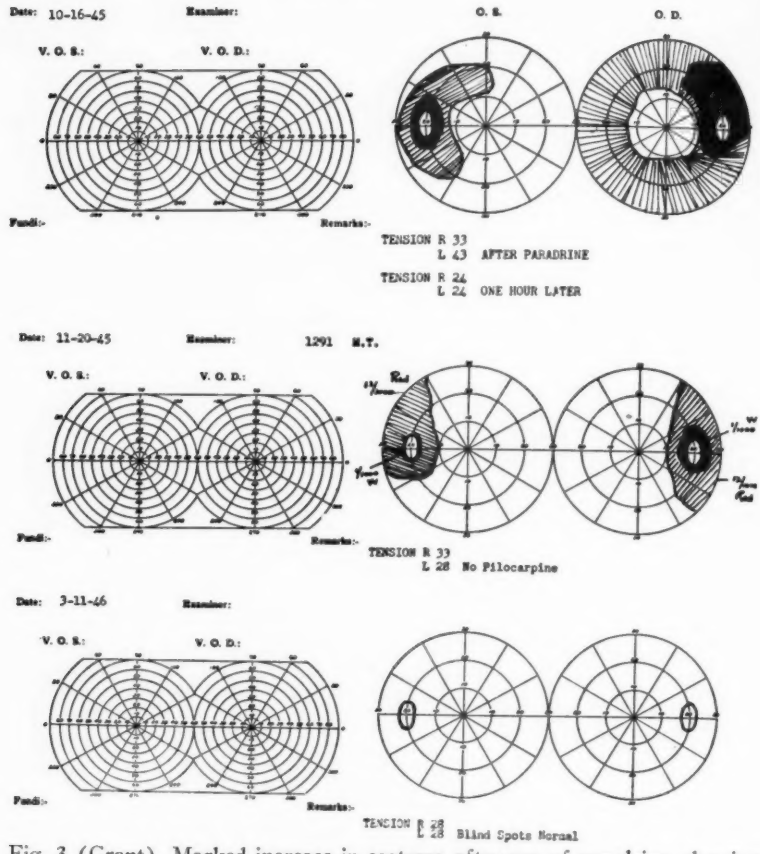

Fig. 3 (Grant). Marked increase in scotoma after use of paredrine, showing very slow return to normal.

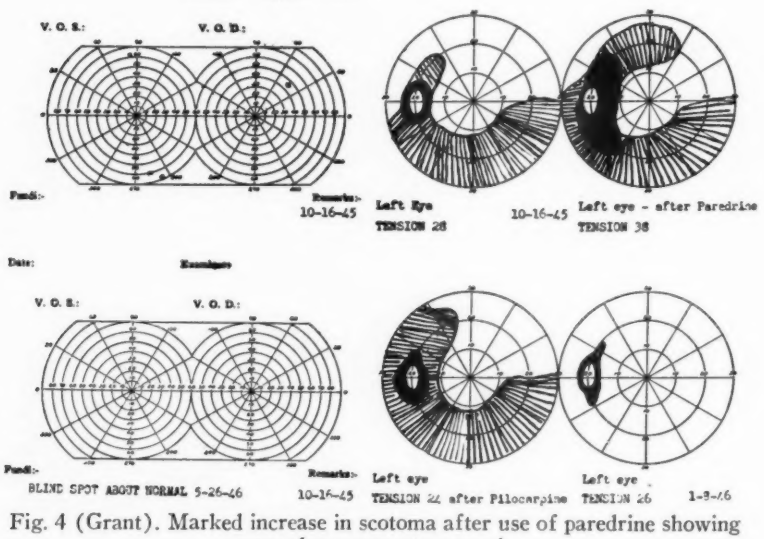

Fig. 4 (Grant). Marked increase in scotoma after use of paredrine showing very slow return to normal.

Case 1. M. T., (1,291), a woman, aged 70 years, has been under observation since 1934. In 1937 considerable sclerosis of the lens nucleus with many streaks in the periphery of the lens was noted. In October, 1945, the vision was reduced to 20/30 in each eye and the tension was normal at noon. One-percent paredrine was instilled in each eye, causing a rise of pressure to: R.E. 43 mm. Hg; L.E., 33 mm. The paracentral field changes at

ELEVATION OF TENSION FOR A FEW HOURS

That a slight increase in intraocular pressure for a few hours each day may occur over a period of years and produce marked changes is borne out by the following case:

Case 3. C. B. R., a physician, aged 65 years, was first seen in 1933. He had been struck in the left eye six years previously by a piece of copper from an exploding rifle shell, which produced an

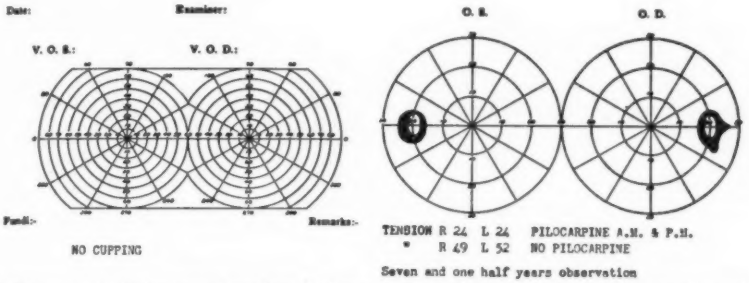

Fig. 5 (Grant). Blindspots of patient 7½ years after observation without cupping of the optic nerve but with marked increase of tension.

that time showed a very marked enlargement and remained so in spite of reducing the tension to 24 mm. in each eye after the lapse of one hour. The blindspots remained enlarged considerably above normal until January 23, 1946, approximately a lapse of three months before they could be considered normal. No cupping of the optic nerve has been present at any time.

Case 2. G. B., (14,167), a woman, aged 67 years, examined in October, 1945, showed a vision of: R.E., 8/200; L.E., 20/25, corrected. The fundus of the right eye showed a retinitis of hypertension, Grade 2, with newly formed vessels on the optic nerve due to a previous vascular accident. There was a slight enlargement of the left blindspot. Paredrine instilled for fundus examination increased the tension to 38 mm. with a marked increase in the size of the scotoma which gradually became normal in May, 1946.

open wound of the conjunctiva but no foreign body was ever found. His vision was 20/20 in each eye and no note was made except a possible slight cupping of the left optic nerve. The tension was: R.E., 20 mm. Hg; L.E., 24 mm. Next observation was in June, 1945, when the vision was: R.E., 20/20; L.E., 20/25. Tension was: R.E. 26 mm. Hg; L.E. 26 mm. Fundi showed slight cupping of both optic nerves. The fields showed slight peripheral contraction, enlargement of both blindspots.

On December 3, 1945, tension was: R.E., 28 mm. Hg; L.E., 28 mm. One hour after the instillation of paredrine, the readings were: R.E., 20 mm. Hg; L.E., 28 mm. On December 5, 1945, on arising, tension was: R.E., 30 mm. Hg; L.E., 33 mm. Fields showed a sickle-type scotoma, detached from the blindspot. This blindspot disappeared in one hour.

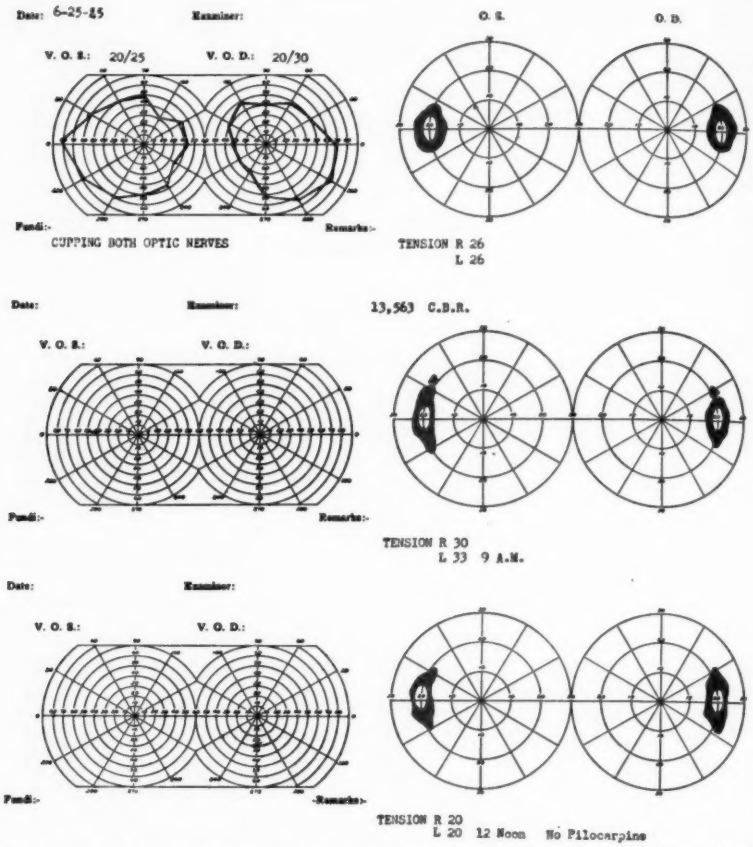

Fig. 6 (Grant). Sickle type of scotoma appearing in early morning, detached from blindspot and disappearing in a few hours when tension became normal spontaneously.

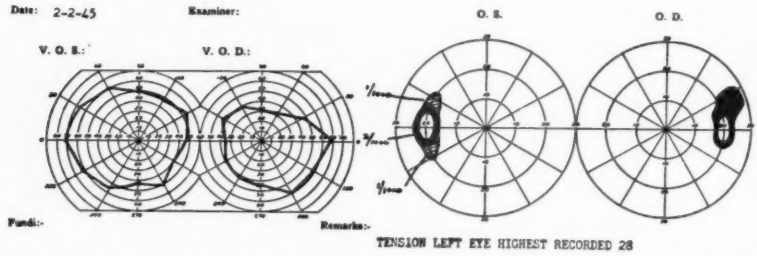

Fig. 7 (Grant). Enlargement of blind spot in shallow chamber with normal tension.

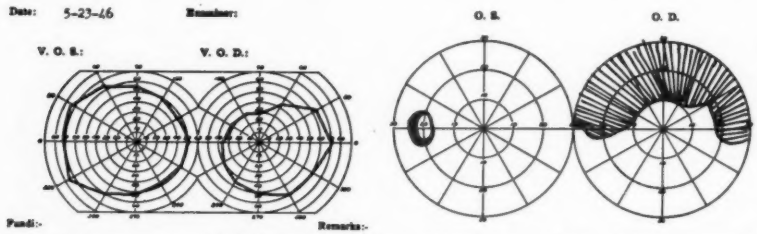

Fig. 8 (Grant). Enlargement of blindspot in shallow anterior chamber without increase in tension.

ENLARGEMENT OF BLINDSPOT WITH NORMAL TENTION

Interest centers chiefly on those cases which Gradle calls the preglaucomatous. In the first instance of the acute congestive type, without increase in intraocular pressure, he states that paracentral field changes are absent. The following

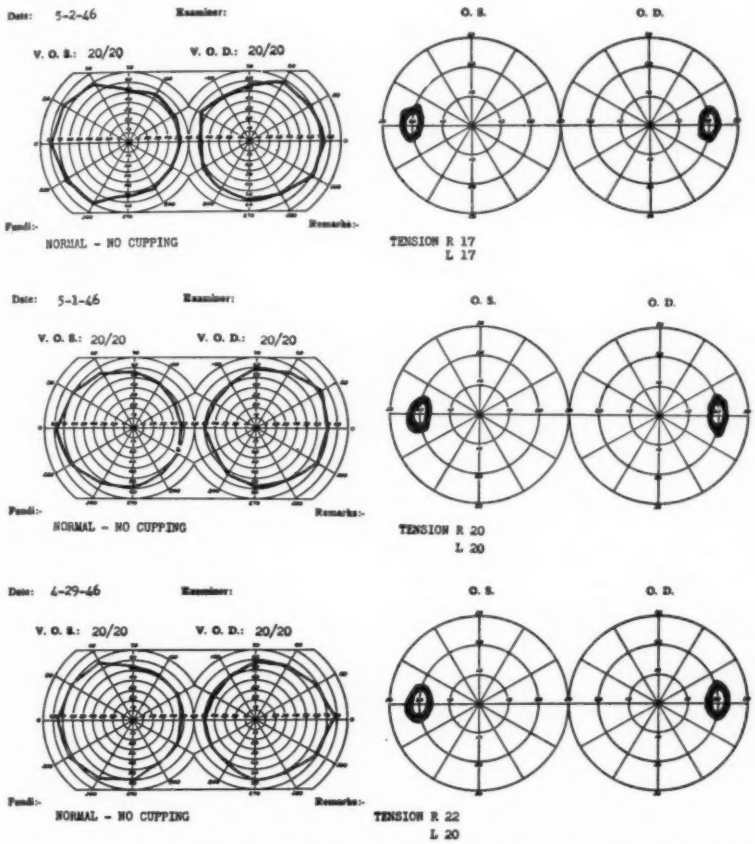

Fig. 9 (Grant). Enlargement of blindspot in three patients with symptoms of glaucoma, but with normal tension.

cases show enlargement of the blindspot with normal tension:

Case 4. J. P. K., a white woman, aged 64 years, was first seen January 19, 1945, with acute congestive glaucoma of the right eye. Symptoms simulating an acute rise in tension had been present since May, 1944. Vision: R.E., 10/200; L.E., 20/20. Tension was: R.E., 55 mm. Hg; L.E., 20 mm. The tension of the right eye was reduced to 20 mm. with 2-per cent pilocarpine every half hour and an iridectomy performed on January 23rd permanently reduced the increased pressure. Records of the 24-hour tension studies of the left eye during her hospital stay did not reveal evidence of increased pressure at any time. The blindspots on January 31 were 2-2-45, 6-14-45, 8-6-45.

Case 5. McK., (14,311), a woman, aged 56 years, reported for examination in November, 1945. The corrected vision was: R.E., 20/20; L.E., 20/20. Tension before mydriasis was R.E., 20 mm. Hg;

TABLE 1

AN ANALYSIS OF 33 CASES OF EARLY GLAUCOMA

Number and Initials	Sex and Age	Vision		Tension No Pilocarpine		Tension With Pilocarpine		Fundi
		R	L	R	L	R	L	
14,385 F.S.	F 75	20/25	20/25	28	28	20	20	No cupping. First degree vascular change
3,090 L.R.	F 48	20/20	20/20	38	38	24	24	No cupping
13,971 M.S.	F 65	20/25	20/25	38	24	20	20	No cupping
9,023 L.B.	F 40	20/20	20/20	33	24	20	20	No cupping
10,067 R.S.	F 55	20/20	20/20	33	24	24	24	No cupping
14,048 F.J.	F 53	20/20	M.O.	33	33	20	24	No cupping. Chorioretinitis left eye, central
1,291 M.T.	F 58	20/20	20/20	33	28	24	24	No cupping. Lens opacities. Nuclear sclerosis
14,012 M.F.	F 55	20/20	20/20	33	33	26	26	No cupping
14,536 M.A.	F 49	20/20	20/20	38	33	24	24	No cupping
416 J.B.	M 46	20/20	20/20	26	26	20	20	No cupping. First degree vascular change
14,418 F.T.	F 49	20/20	20/20	33	17	20	17	No cupping
4,950 B.S.	F 70	20/20	20/40	33	33	24	30	No cupping. Second degree vascular change
2,642 F.G.	M 47	20/20	20/20	38	24	20	24	No cupping
10,714 C.B.	F 52	20/20	20/20	33	26	20	20	No cupping
14,167 G.B.	F 68	8/200	20/20	33	33	28	26	No cupping. Retinitis of hypertension third degree right eye
5,316 F.T.	F 50	20/20	20/20	28	28	20	20	No cupping
8,356 H.B.	M 57	20/20	20/20	33	17	17	20	No cupping. First degree vascular change
5,392 F.C.	F 59	20/20	20/20	38	28	26	26	No cupping. First degree vascular change
6,136 F.M.	F 72	20/30	20/30	38	24	20	20	No cupping. Marked nuclear sclerosis
14,782 W.C.	F 60	20/20	20/20	33	33	28	28	No cupping. Second degree vascular change
14,910 C.J.	M 48	20/20	20/20	28	33	24	24	No cupping
3,400 J.O.	F 45	20/20	20/20	52	50	20	20	No cupping
3,020 L.R.	F 57	20/20	20/20	38	26	24	24	No cupping
10,983 J.R.	F 46	20/20	20/20	38	17	20	20	No cupping
5,515 W.S.	F 58	20/20	20/20	33	26	20	20	No cupping. First degree vascular change
10,013 E.S.	F 73	20/20	20/30	33	28	20	17	No cupping
12,511 T.W.	F 60	20/20	20/20	28	28	20	20	No cupping
13,563 C.R.	M 66	20/20	20/25	30	33	14	14	Cupping both optic nerves
12,746 J.K.	F 64	20/20	20/20	55	28	20	17	Acute glaucoma right eye Shallow chamber left eye
14,311 W.M.	F 56	20/20	20/20	24	20	17	17	Acute glaucoma right eye Shallow chamber left eye
5,300 B.L.	M 60	20/20	20/20	17	17	17	17	No cupping
9,600 H.M.	M 43	20/20	20/20	17	17	17	17	No cupping
14,212 E.D.	F 45	20/20	20/20	20	17	16	13	No cupping

L.E., 20 mm., and after mydriasis: R.E., 24 mm. Hg; L.E., 20 mm. Five-percent pilocarpine was then instilled in each eye. The following morning there was pain and blurred vision in the right eye which required surgery for the control of the tension. Vision was ultimately 20/20 with some reduction of the visual field. During her stay at the hospital, the tension of the left eye was normal throughout the 24-hour period and was never found to be elevated. There had, however, been symptoms suggestive of an acute rise of intraocular pressure. The cham-

ber was slightly shallow and a definite enlargement of the left blindspot was noted on discharge from the hospital, and the highest tension recorded has been 20 mm. This enlargement has persisted in spite of the use of pilocarpine twice daily.

Comment

Of the chronic noncongestive type of questionable glaucoma, three cases are here presented. The ages of the patients were 43, 45, and 59 years. All complained of fatigue with adequate correction of the refractive error. In two there was unequal accommodation, and in the other the accommodation was a very low normal. All three had enlarged blindspots, normal tension, and normal fundi. All three were very definitely improved with 1-percent pilocarpine used twice daily and were very willing to continue because of the relief obtained. The enlargement of the blindspots is characteristic of the group with increased tension, and the two with shallow anterior chambers. No change has been noted in the size of the blindspot in the course of a few months' treatment.

There are many questions. Is this a glaucoma with changes due to low pressure? Are the changes in the blindspot due to pressure? Has the tension been elevated above normal at some previous time? These questions can only be answered by long-continued observation and study.

Summary

The following cases are presented: An analysis of the enlarged blindspot in 27 cases of early glaucoma without cupping of the optic nerve or peripheral field changes. A case of slight cupping of the optic nerve with increased tension found on only one occasion in the early morning with characteristic changes of glaucoma. Two cases of acute congestive glaucoma, with shallow anterior chamber in the fellow eye, with normal tension and an enlargement of the blindspot. Three cases of enlarged blindspot in persons with symptoms suggestive of glaucoma, without evidence of increased intraocular pressure. Study of the blindspot is a valuable aid to the study, progress, and diagnosis of early glaucoma.

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THE DISSATISFIED REFRACTION PATIENT*

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Study of the physical laws of refraction is an exact science. A less scientific procedure is the estimation of errors of ocular refraction. In this act, colloquially and ungrammatically referred to as "refracting a patient," the introduction of the subjective element involves fallibility. In the main, the objectives of clinical refraction are: (1) improvement in visual acuity, in which case the result of subjective improvement can be expressed by an objective formula; and (2) the relief of completely subjective symptoms. In the last instance the prescribing of corrective lenses becomes an art entailing its proper modicum of woes.

As practitioners of medicine our obligation to the patient is not fulfilled until he is relieved of his symptoms and satisfied in his own mind. The mere issuance of a written optical formula accompanied by certain brief instructions may possibly result in a cure; but this discussion concerns itself with the patient who is still unhappy and occasionally belligerent. Let us treat the patient as an ill individual; not merely compensate for his refractive error. We are, let us hope, physicians, not physicists.

On the lower plane of economics these patients deserve special consideration. A loquacious and dissatisfied patient does one's practice considerable disservice, especially in smaller communities. It is business folly to refuse to see these people or to brush them off with a curt statement that "your glasses are correct and you will have to get used to them."

In actual practice the receptionist and, embarrassingly, those in the reception room are the first to hear of one's failure. The receptionist should receive the news sympathetically and diplomatically usher the patient to more secluded surroundings. Here he may be allowed to cool off, but not too long, for he may be irked by delay.

The complainant frequently begins with a deluge of generalities, sometimes highly seasoned with maledictions for the glasses and opprobrium for the doctor. On receiving the patient in the consulting room, it is my practice to give him ample time to relate his woes, and I list each one. This conversational catharsis tends to relieve antagonism as well as to define specific difficulties which may be explained or corrected.

Blurred vision

In any complaint the first procedure is obviously to check the lenses for agreement with the prescription. This has presumably been done before they were worn but errors do occur, especially reversed axes, reversed lenses, and less frequently a totally strange correction. If the lenses are correct and the complaint is lack of visual acuity, especially if the patient claims to see better with his former correction, find out if this is so and at what distance. Not infrequently a sense of strangeness is interpreted as blurring and, if improved vision can be demonstrated, the complaint is resolved. If the vision is definitely less than when the glasses were prescribed, assuming no ocular disease, there is obviously an error. With lenses prescribed under mydriasis a further reduction in sphere may be necessary, or the axes may have

* Read at the 82nd annual meeting of the American Ophthalmological Society, San Francisco, California, June, 1946.

shifted, especially if the cylinders be of high degree. Too much spherical correction is more frequent with high hypermetropia, but can occur with corrections of less than +1.00D., and also in low minus corrections. One patient accepting −2.00D. at 6 meters found his vision for bowling impaired until another quarter was deducted. Shifting of axes after mydriasis is frequent. Both these difficulties could be avoided by routine postmydriatic tests, but the delay, in patients living at a distance, is prohibitive.

A discrepancy between the location of a focal plane in the trial frames and the finished glasses may cause blurring with high corrections. A clue to this is furnished when the patient either pulls the glasses down on his nose or pushes them nearer his eyes to improve his vision. This is particularly true in aphakia or very high myopia. A young woman for whom I had prescribed −18.00D. had to be increased to −19.00D. because I had placed the test lenses too close to her eyes, resulting in undercorrection. When using high spheres, it is essential to consider which cell of the trial frame is used.

A not infrequent complaint is that the formerly better eye is now the worse eye. If, with the former correction, the vision in O.D. was 6/9 and in O.S., 6/15, and on refraction the right eye was unimproved and in the left eye 6/7.5 was obtained, the patient feels there is something wrong. An explanation of the pathologic processes will usually satisfy the patient. In intumescence of the lens, a similar complaint results when the distance acceptance is toward the minus side, thus making the reading focus more remote. The myope, especially if presbyopic, will often complain of reading difficulties if the strength of the distance correction is increased.

Often we hear the statement: "I could see all right without glasses until you gave me these." The explanation is either that accommodative strain has been relaxed or the patient is approaching presbyopia, or a change of occupation is entailing more accurate vision. It is with difficulty, however, that one can convince the patient that the glasses have not "weakened" his eyes.

All cases of blurring are not the fault of the recently prescribed lenses. In two instances, both women, one presbyopic and one younger, the complaint was inability to read with the new glasses. The disability was real. They both required addition plus. There was a marked weakness of accommodation, in the first instance due to "nerve medicine" containing hyoscine, and in the second to gastrointestinal therapy containing atropine.

Clerical error

If none of the above be applicable, it is necessary to suspect a clerical error. It is a great help to have a record of a previous refraction. If the patient is new to me I always neutralize his old lenses, both to avoid putting him to the expense of duplication and to find with what correction he has been unhappy. Even with assiduous attention to accuracy the human mind plays tricks especially under pressure. Mental transpositions can occur; for example, in recording axes, transposing 15° to the right of the vertical to 15° to the left of the vertical, thus recording 105° for 75°, or similarly with a horizontal axis; or transposition of the intercardinal axes. A substitution of the wrong sign should be easily found if it occurred in transcription. If it is in the original record, a comparison with former corrections furnishes the clue. If there be no former record, it is necessary to repeat the refraction. Clerical errors can cause the omission of a figure, axis 135° being recorded as 35°, or an incorrect figure in transcription such as a hastily

written 5 being read as an 8. In one instance, I discovered a +1.75D. add in a person 75 years of age. Obviously, I had meant a +2.75D. In dictation, a figure may be miscalled or misunderstood. In recording from the trial frame when more than two lenses are used, one may be overlooked. The most grievous error I have ever encountered was a reversal of 4 degrees of vertical prism! This was discovered by comparison with previous corrections.

Blurring, of course, can arise from ocular disease. The patient is usually aware of corneal opacities as they have resulted from antecedent disease or injury. Lenticular opacities, cloudy vitreous, or macular degenerative changes require explanation, and it is often difficult to convince the patient that the fault is not remediable by different lenses.

Adjustment

Passing now from blurring to discomfort, the first step is to check the adjustment of the glasses. The interpupillary distance and the optical centers must correspond, with proper decentering for reading corrections. There must be vertical compensation for facial assymetry, and the difference in level of the lenses must be accomplished without rotation of axes. In high corrections it is useful to check the adjustment of the finished glasses by the Maddox rod with horizontal image. In high cylinders I have found it useful to check the axis of the finished glasses with the cross cylinder. Minute degrees of rotation which cannot be measured on the trial-frame scale will result in comfort or discomfort. I have the optician come to the office and make repeated checks until the point of equality is found.

Some persons are more comfortable with an incorrect P.D. One hypermetropic person with high esophoria is comfortable only with the lenses decentered in. This gives the effect of base-in prisms which theoretically should increase discomfort, but does not.

Complaints based on obvious mechanical difficulties we will pass over. Comfort and convenience are often increased by raising, lowering or tilting the lenses. The latter is especially true in bifocals. If, on looking down, the reading segment is progressively farther from the cornea the effective strength of the lens is increased, causing blurring or an inconveniently short focus. This is obviated by tilting the lower edge toward the face so that the radius of the eyeball plus the distance from corneal center to lens becomes an approximate constant.

Complaints of distortion, horizontal lines having a curve, the table or street not being level, the sensation of feeling too tall or too short and stepping too high to clear the curbstone are familiar to all of us. They are due to unaccustomed degrees of correction, unfamiliar cylinders, or spherical aberration through the periphery of lenses. Explanation and time resolve these difficulties.

Anisometropia entails difficulties. An obviously impossible combination should not be prescribed. The possibility of discomfort can often be foreseen and, if the patient is forewarned, a subsequent necessary reduction in strength of the offending glass presents no embarrassing difficulties.

Reflections

Reflections cause bitter complaint from some individuals. This is especially frequent with low minus corrections, where the total spherocylindrical strength is within 0.50D. or 0.75D. I have tried various transpositions without benefit. Recently the Balcote film has become available for civilian use. This reduces the reflected light from approximately four

percent to less than two percent and affords some measure of relief. I have not had an opportunity to try it in those individuals who complain of four headlights on an approaching car gradually merging to two.

Muscles

Discomfort from disturbance of the accommodation-convergence reflex is common. An increased plus correction either for distance or near entails a relative increase in convergence and relaxation of accommodation, and conversely an increase in minus entails more accommodation with no increase in convergence. This is more frequent in the farsighted person or presbyope and is especially marked with convergence insufficiency. Time will often adjust matters and explanation helps the patient's state of mind. If convergence insufficiency is present, appropriate exercises are of great help. In an occasional case I have prescribed prisms base in for close work, but this is without remedial virtue and should be avoided if possible.

If vertical prisms have been prescribed, there may be overcorrection because the finding was temporary, possibly due to vertical maladjustment of former lenses, or because the measurement was made with maladjusted trial frames. If the Maddox rod shows overcorrection in the finished glasses the prism must be reduced or eliminated. The patient may be wearing the glasses intermittently and he may experience confusion each time they are put on or removed. The vertical muscle imbalance may not be concomitant so that the prism is incorrect for certain frequently used directions of gaze. Latent muscle imbalance may be present to be revealed by cover testing. Several times I have found the covered eye to turn up whichever it be; that is, right hyperphoria manifested by occluding the right lens and left hyperphoria by occluding the left lens. Unless the hyperphoria remains on the same side with either eye occluded, I do not use a vertical prism.

Presbyopia

Presbyopia entails its peculiar pitfalls. In the incipient presbyope it is essential to avoid bifocals until they are necessitated by the conditions of ocular use of the particular individual. An addition for near may be of comfort for prolonged close work but a bifocal for constant wear will not be satisfactory if there be not a distinct improvement in visual acuity with the lower segment. A bifocal is a crutch. He who can walk without a crutch will not use one. There must be sufficiently distinct improvement for the aid to be appreciated. In this regard, housewives are a particular stumbling block. I make it a custom, with infrequent exceptions, not to prescribe bifocals until housewives cannot see the print in the telephone book. By that time it is a nuisance to run upstairs for the reading glasses and all is well.

The focal distance of the addition for near must suit the patient's occupation and, of course, the older he is the more important it is to place the remaining accommodative range at the most serviceable distance. Stenographers want to see their copy, see the typing and still read at a reasonably (or unreasonably) close range. Carpenters want to see their thumb on starting a saw and the far end of the board, and still have clear vision at infinity and for reading. Music teachers want to read, play the piano, stand behind their pupils, and still have the piano score clear. Violinists want to read music on a distant stand and see the conductor. A lumber grader achieved relative comfort from trifocals. Timber cruisers have to be able to see their notations but are bothered by the lower segment when

walking a rough trail. Store clerks complain that they have to stoop to write sales slips and can't see the price tags on shelves through the upper segment. A similar difficulty exists for postal employees sorting mail. Dentists work at a very close range. Otologists must have a segment that will come behind the head mirror aperture. A refractionist must be able to see the trail frames without tilting his head back and an ophthalmic surgeon must have acute vision at his customary working distance.

This is all related to the most frequent complaint arising from bifocals; namely, blurring in the intermediate distance which increases with each successive increase in aid. Some patients are satisfied with an explanation. Many require a careful analysis of the various conditions of their ocular work. The difficulties can be met by segments of different heights, separate glasses for specialized purposes, or, less frequently, by trifocals. It takes time to analyze the person's needs and to evaluate his personality. It takes ingenuity to solve some of the more complicated demands. Starting with the premise that glasses can be made to give clear vision at any given distance and direction of gaze a solution can usually be found. Sometimes the patient does not have the adaptability or stamina to accustom himself to the prothesis.

The most common mistake is to overcorrect the presbyopia. Despite assiduous care and a constant awareness of this danger it still happens. When encountered, unless it is due to lack of tilting as previously mentioned, admit the fault, smile charmingly, commiserate with the patient, and obtain new lenses. It is more likely to happen when the acceptance for 6 meters shows increased plus and the addition for near is also stepped up. For example: A patient has been wearing +1.50D. with a +1.50D. add, making a total of 3.00D. He now accepts +2.00D. for distance and being older you increase the add to 2.00D., making a total of +4.00D., and he finds the reading distance too close. When the plus acceptance for distance increases, the patient may be comfortable with no increase in the addition for near.

On the other hand, with lenticular intumescence the patient has frequently accustomed himself to read at 9 or 10 inches. With an increased minus lens for distance and an addition appropriate for his age allowing him to read at 14 inches, he is dissatisfied. These persons desire excessively strong lower segments, particularly if lenticular opacities are present, in order to obtain a larger image.

Inequalities in accommodation will account for some complaints and should be compensated. In a unique instance, in incipient presbyopia without discoverable organic disease, to explain a unilateral accommodative weakness I prescribed reading glasses with a unilateral addition and achieved success.

Some patients will complain of blurring across the room. They have become accustomed to clear vision at this distance by wearing an overcorrection for infinity. They are happier with an extra quarter or half diopter in the upper segment even though it blurs somewhat at the horizon.

Elderly persons with lenticular opacities sometimes expect miracles. With the old glasses they may have had only 6/15 vision and with the new, 6/9+, but they are dissatisfied that the visual acuity of youth is not restored. To explain is simple; to make them contented is difficult, especially if complicated by the hardheadedness of cerebral arteriosclerosis.

Occasional persons will not persevere with cylinders until they are unconscious of them. This is particularly true of the advanced presbyope who is wearing glasses for the first time. It is sometimes

better to remove the cylinders at the sacrifice of some visual acuity, and it is always better to do so before a smart competitor does it for you.

Rapid changes in refraction may be due to glycosuria but there is an occasional patient of advanced years who will accept radically different corrections on repeated examination. The first having proved unsatisfactory, the individual returns, and after the usual sleuthing, you repeat the examination with a markedly discrepant result. I have recently been a near candidate for commitment because a woman, aged 72 years, would vary in the left eye from a minus 0.5D. cylinder to a plus 1.00D. cylinder with the axis ranging from 180° to 45°. The prevention is repeated refraction before prescription. The solution is to give the weakest possible cylinder with which good vision is obtained. The final axis is probably an approximation but will be more accurate if testing be intermittent and not pressed to or beyond the point of fatigue, and will be progressively less important as the cylinder is reduced.

Special problems

Aphakia presents its special problems. In monocular aphakia, comfort can be increased by occluding the less serviceable eye with a frosted glass or black paper. The absence of accommodation (with very rare exceptions), the necessity of thick lenses, and the consequent aberration combined with the age of the patient require considerable stamina and adaptability and frequently much explanation on the part of the physician. I believe many persons are happier with visual acuity of 6/12 and 6/45, with binocular vision and an ordinary correction, than with 6/6 or 6/5 and monocular vision with a thick lens. For this reason (and others) I do not rush into extraction of partially cataractous lenses. One bilateral postoperative cataract case complained of both vertical and horizontal diplopia after the second eye was corrected. The vertical error was relieved by proper adjustment of lenses and the horizontal by convergence exercises.

A few unique situations deserve special mention. A letter from a patient wearing bifocals stated he could not see bulletin boards. Correspondence failed to clarify the difficulty. When he returned to the office, the situation was this: He was deformed with spinal arthritis so that his head was inclined forward. In order to bring his eyes to bear on the bulletin board he had to lean back against the opposite wall. This placed the bulletin board in the intermediate blurred area. The difficulty was resolved by a pair of "fit-overs" of the proper focal distance.

Another patient has a slight paresis of the left external rectus, due to which he is accustomed to hold his head slightly rotated to the left. He had never been able to wear bifocals with comfort. By decentering each lens one millimeter to the right he was relieved.

A patient, with an inferior surgical coloboma of the left eye resulting from trauma, was bothered by dazzling. He had no discomfort in the uninjured eye. A prescription incorporating a clear lens for the normal eye and a No. 4 soft light for the injured eye gave relief.

Nonrefractive asthenopia

Improper lighting explains some cases of persistent complaint. Fluorescent lighting is particularly at fault, less so now, but it is far from perfect. Insufficient or excessive light in relation to the work performed may be the cause. Sufficient light for reading is insufficient for drafting, or picking flaws in metal specimens, or sewing black cloth with black thread. Excessive light may be tiring. Concentrated, circumscribed illumination

may cause "spotlight fatigue." According to Ferree and Rand, an extreme contrast of 1:50 is the limit of tolerance. I believe it is lower. Glare may be direct, reflected, or due to improper relation between source and object. Complete search for the abstruse causes of asthenopia should include a survey of the patient's environment with a light meter. This is, of course, impracticable.

Systemic disease may be the answer. Ocular function requires muscular activity and any systemic fault which lowers muscular tone, from anemia to myasthenia gravis may produce asthenopia. Close work in excess of the individual's capacity may produce simple fatigue. The menarche and menopause cause a manifestation of symptoms otherwise disregarded. A child may have psychologic reading or writing problems unrelated to refraction error. There may be vitamin-A deficiency. Nasal congestion, obstruction, or sinus infection may produce symptoms indistinguishable from refractive asthenopia.

Or there may be aniseikonia. I mention this to avoid the criticism of omission. I am unable to distinguish the symptoms of this disorder from those arising from refractive error or muscle imbalance, and am geographically located so that I have no experience therewith.

General remarks

It is true that some persons do not have the stamina to accustom themselves to glasses. They have similar difficulty with dentures, wooden legs, crutches, and new shoes. There is a little of this trait in all males who love to hang on to an old hat. However, it is easy to label the patient neurotic or neurasthenic and this should never be done without exhaustive investigation. Even then I would rather consider him hypersensitive. I believe it has been established that some individuals actually feel more pain from a given stimulus than others. Aesthetically it is certainly true that some individuals are offended by inharmonious colors more than others. In the realm of sensory stimulation, but at the other extreme, some people live in contented symbiosis with pediculi while others are much disturbed by the stimuli of these "poor weak timorous beasties." Or consider the classical example of the man in bed New Year's morning, suffering from postimbibition syndrome and cringing from the raucous cacophony of the kitten stamping across the Persian carpet. My point is that we must consider the threshold of pain or discomfort in a given individual, seek out any discoverable cause by exhaustive search, and correct it if it be remediable, before we consign the patient (with private imprecations) to a life of travail wandering in an ever widening orbit from refractionist to refractionist.

Many causes of dissatisfaction can be obviated at the original examination. There is occasionally an obvious clash between the personality of the doctor and the patient. I know of one instance where a difficult female was taken aside by the office nurse and told, "Oh, please don't make doctor angry; it upsets him so!" Obviously, she never thought she had been properly refracted. The tempo of the refraction must be adjusted to the patient's ability to perceive difference and his reaction time. It is unwise to rush a person without training in visual distinction. It is easier to refract a surveyor or a microscopist than a chef. It is quicker to refract a Latin than a Scandinavian. Some persons apparently can't perceive a difference of a half diopter. Others can split an eighth and consistently estimate an axis to 0.5 degrees. Some patients are obtuse and indifferent and fail to register gross differences. Others are apprehensive, afraid of giving inconsistent an-

swers, and can always find a difference between a +0.12D. and a +0.12D. To avoid later complaints assure the patient of the correctness of his answers. Adjust the tempo of the procedure to the reaction time of the patient. Create no impression of hurry. When the prescription is given, foresee as many difficulties as possible due to any of the reasons touched upon in the foregoing and life will be a little smoother. And if the patient returns dissatisfied, accord him every courtesy and all the facilities at your command to restore him to health, which means, by one definition, to put him in perfect accord with his environment.

Summary and Conclusions

1. The dissatisfied refraction patient deserves our time to hear his complaints.
2. Usual and unusual causes of complaint are grouped and discussed.
3. Every effort should be made to locate the difficulty and correct it.
4. A patient explanation of irremediable difficulties should be made.
5. The obligation of the refractionist is not discharged until the patient is comfortable in his eyes and contented in his mind.

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PROCEEDINGS OF THE ALL-INDIA OPHTHALMOLOGICAL SOCIETY

Session 1945, Volume 8

This report contains the transactions of the scientific sessions, minutes of meetings, and membership lists. The first part of the program was a symposium on glaucoma dealt with by six writers from the point of view of etiology, symptomatology, treatment, the Bengal epidemic of dropsy glaucoma, and gonioscopy. Epidemic dropsy glaucoma is one of the main ocular complications of epidemic dropsy. It was first recognized by Maynard in Calcutta in 1908. The incidence increased greatly until 1935. It is a primary chronic noninflammatory glaucoma.

The topics of the other 23 papers on the program are as varied as one would expect when a large number of ophthalmologists with varied interests and practices convenes. Some papers are case reports and are strikingly brief. Several deal with experience with sulfa drugs. A discussion on tuberculin therapy by S. N. Cooper is one of the longer essays. The author gives a comprehensive and thorough analysis of the essentials of our knowledge of tuberculin. He favors the therapeutic use by desensitization and states that "the eye, being an organ which exhibits the immune-allergic reaction easily, is a very sensitive balance to watch the reaction of tuberculin and for determining the dosage required for desensitization."

F. H. Haessler.

NOTES, CASES, INSTRUMENTS

BILATERAL OPHTHALMOPLEGIA IN ACUTE ANTERIOR POLIOMYELITIS*

EDWIN S. WRIGHT, M.D.
Glendale, California

The case to be reported is of unusual interest since it is a description of a rare condition; that is, bilateral complete ophthalmoplegia in acute anterior poliomyelitis.

Paralysis of the extraocular muscles in acute anterior poliomyelitis is not uncommon. Sautter[1] found that 19 of 669 cases of this disease exhibited symptoms of paralysis of one or more extraocular muscles. He stated that Medin found 9 cases of paralysis of one or more extraocular muscles in 64 cases of the disease; Wickman found 22 isolated cranial nerve palsies and 34 combined cranial and spinal nerve palsies in 862 cases; Leegard reported 2 cases of facial palsy, 3 cases of extraocular muscle palsy with spinal symptoms and one of ptosis with spinal symptoms in 311 cases; E. Mueller in 100 cases found 13 palsies and 3 unilateral abducens palsies.

In the New York epidemic of 1907,[2] an analysis of 752 cases showed 27 facial, 18 lid palsies, and 26 cases of strabismus. Emmons[2] found in 70 cases of the disease 7 cases of extraocular muscle paralysis and concluded that as a safe average, 10 percent of cases of acute anterior poliomyelitis show symptoms of paralysis of the extraocular muscles.

Ophthalmoplegia in acute poliomyelitis is, however, very rare. Sautter[1] recorded one case of bilateral ophthalmoplegia externa with ptosis in the left eye. Posey and Swindells[3] reported one case of complete bilateral external ophthalmoplegia in this disease. They cited Wickman as reporting a case from the Vienna epidemic of 1909, in which there was ophthalmoplegia with preservation of convergence, and they cited Takahashi as reporting a similar case from the same epidemic, and Uthoff as having seen one case of external ophthalmoplegia in acute anterior poliomyelitis.

Emmons[2] did not report such a case in his series. Hall's case[4] did not exhibit ophthalmoplegia. Ghormley[5] does not mention it in his series of 125 cases, but he was primarily concerned with optic neuritis. Somerset,[6] writing on the various causes and clinical manifestations of ophthalmoplegia externa, does not mention poliomyelitis although he cites a case of conjugate deviation with ptosis which he considered due to an old encephalomyelitis. Poe[7] described a case of ophthalmoplegia totalis, but concluded it was congenital in origin.

Reference to this symptom complex in textbooks of ophthalmology or neurology is scanty and not very illuminating. Acute anterior poliomyelitis is mentioned as a possible cause of ocular-muscle palsies by Peter.[8] Berens[9] mentions Wernicke's superior polioencephalitis as a cause of ophthalmoplegia, but Emmons[2] believes this is not an entity but is in reality infantile paralysis. Rea[10] states that acute nuclear paralysis is due to an acute inflammatory process in the nuclei resembling that which produces poliomyelitis, or to hemorrhagic lesions. In his description of the ocular effects of acute poliomyelitis, ophthalmoplegia is not mentioned. Wechsler[11] does not mention ophthalmoplegia in poliomyelitis.

The pathology of acute poliomyelitis is better known. Charcot[16] was apparently

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the first to appreciate the significance of the anterior horn-cell degenerations, and his hypothesis of the organic lesion of poliomyelitis has, since 1941, challenged the ingenuity of all students of the pathology and pathogenesis of this disease. Roth[16] thought the essential lesion was primarily an interstitial myelitis originating in the glia and the vessels. Rissler's work[16] showed both changes simultaneous and dependent.

How does it happen that many apparently severe paralyses in the acute stages later recover good function? Flexner and Amoss[16] answered this when they stated: "There are good grounds for believing that a considerable part of the paralyses, especially those that are not permanent, are the effect of temporary vascular impediments. The impediments are all outside the lumina of the vessels which are merely reduced in caliber through pressure; thrombi do not occur. Some of the functional disturbances are possibly, thus, anemic in origin; others are probably caused by slight degenerations and still others are undoubtedly caused by focal hemorrhages and edema. All these effects may, possibly, be recovered from; part by isolation of the cellular vascular infiltrate and re-establishment of the lumen, part by absorption of the edema and hemorrhage, and part by restoration of the mildly degenerated nerve cells. The severer degenerative and other lesions, through which actual necrosis is produced, do not become restored."

Hassin[13] gives three features of the disease; namely, exudation, alteration, proliferation. The exudation is represented by perivascular infiltrations, the alteration by ganglion-cell degeneration, the proliferation by progressive glial phenomena and nodule formation. The morbid changes may extend throughout the entire central nervous system and become a disseminated condition.

In the early stages, the anterior horns are swollen, areolar, and vacuolated; in severe cases, there may be foci of necrosis and hemorrhages. The ganglion cells show

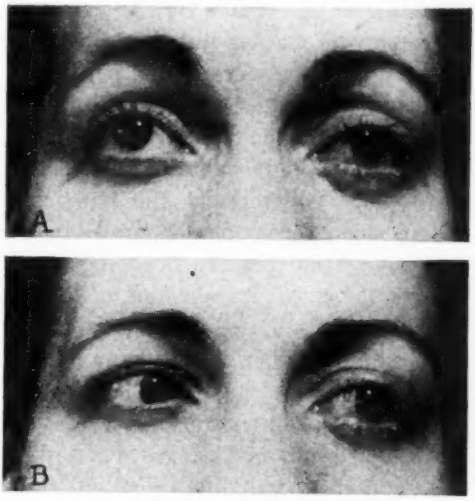

Fig. 1 (Wright). (A) Eyes front showing a slight divergence. No motion was observed on attempting vertical movements. (B) Attempting to look to the left. The right medial rectus was the only muscle functioning, and its action was paretic.

chromatolysis, tumefaction, and invasion by phagocytic elements. In other cases, they are merely surrounded by satellites but not invaded. The ganglion cell may disappear within 24 hours. Glial cells increase enormously in number, both oligodendroglia and microglia. Parallel with the ganglion-cell destruction and glial changes are demyelination of white fibers of the anterior horns. In advanced cases both axone and myelin are replaced by glia. This also occurs in the anterior roots. The entire lower motor neuron succumbs in a short time.

Independent of these parenchymatous changes are changes (mesodermal) in the meninges and blood vessels. There is hyperemia and round-cell infiltration, mainly of lymphocytes, and, later, plasma cells and polyblasts. These cell bodies are con-

fined to the Virchow-Robin spaces but in severe cases may invade parenchyma.

Although as a rule the changes are confined to the cord, in epidemics or severe forms the clinical picture may assume the ascending or descending type of Landry's paralysis with marked involvement of the medulla, pons, mesencephalon, basal ganglia, and even cortex. The condition may be so marked in the cortex as to be histologically indistinguishable from epidemic encephalitis. Mesodermal and parenchymatous changes may not be parallel in degree but are independent phenomena due to the same cause. Localization of lesions in poliomyelitis and epidemic encephalitis may be similar; that is, substantia nigra.

Wernicke's description of hemorrhagic superior encephalitis as given by Hassin[13] shows hyperemia and neovascularization, degeneration of ganglion cells, and reactive glial proliferation mainly around the third ventricle. In some cases, the degenerative changes are found in the nuclei of the medulla and cranial nerves.

Case report

The following case report is that of a patient ill of acute anterior poliomyelitis during the epidemic that occurred in the Chicago area in the summer of 1946.

Miss M. R., aged 24 years, white, student nurse, entered the hospital on September 18, 1946, complaining of dizziness, diplopia, vicelike headache, and nausea. Slight nausea and dizziness had been present for five days prior to admission, but diplopia occurred on the day of admission. The preceding summer she had had intermittent headaches and nasal stuffiness, and a diagnosis of hay fever and upper respiratory infection had been made. Three weeks prior to admission she had had a severe upper respiratory tract infection, but went on a visit to Canada. On returning she began to notice the symptoms given above.

Examination showed, on admission to the hospital, enlarged cervical glands, neck somewhat stiff, with pain elicited on its movement; tonsils large and inflamed. The pharynx was inflamed and showed hypertrophied lymph follicles. Lungs showed moderate increase in breath sounds bilaterally and resonant percussion. Abdomen showed a right, lower-quadrant scar and no tenderness nor rigidity. Reflexes were: Abdominals present, biceps and triceps equal but diminished, knee and ankle jerks active and equal. Temperature was 103° F.; pulse, 120; respirations, 24.

Ophthalmic examination revealed no nystagmus. Both eyes were deviated outward, although the left eye deviated less. Each eye retained a weak power of external rotation and could make feeble vertical movements when abducted. Convergence was absent, but there was still some activity of the medial recti since on covering alternate eyes the uncovered eye swung back from abduction to fix near the midline. Both pupils were small but responded feebly to light. The patient could not read 12-point type at any distance.

Spinal fluid findings were: Total protein 86.8 mg.; W.B.C. 58 (60 percent lymphocytes; 40 percent polymorphonuclear leukocytes). Five days later the spinal fluid findings were the same plus a negative Kahn and a gold curve of 1-1-2-2-2-1-000.

Nose and throat cultures showed Staphylococcus albus and aureus, diphtheroids, pneumococci, and M. tetragenous.

The blood count was: R.B.C., 4,730,000; W.B.C., 10,350 (with 71 percent filament neutrophils, 7 percent eosinophils, 1 percent basophils, and 21 percent lymphocytes). The urine was normal.

Six days later, bilateral ptosis was noted as well as weakness of the muscles of the

back and of the extremities. Two weeks after the onset, ophthalmoplegia was complete in both eyes and a left seventh-nerve paralysis had developed which resulted in inability to close the left eye. Voiding had also become difficult. The facial-nerve lesion then slowly regressed so that 2½ weeks later the patient could close the lids to within 2 mm. of each other. Six weeks after the onset of the disease, the right eye could be adducted 20 degrees and the left eye could be adducted 15 degrees and could hold fixation better than the right. Vertical movements were almost nil. Eight weeks after onset, the patient was suppressing in the right eye and fixing with the left, and monocular adduction had largely returned. Pupils had returned to normal and accommodation was sufficient to read 8-point type at 13 inches unaided. Convergence remained nil. A severe weakness of all muscles of both hands remained. Both deltoids and triceps remained paralyzed. There was left wrist drop and bilateral foot drop, worse on the left. Six months later the right medial rectus was functioning; the left medial rectus was paretic, and scarcely any motion had returned to the vertical muscles. Convergence was nil and the wrist and foot drop remained severe.

The patient received a total of 2,820,000 units of penicillin, 12 gm. of sulfadiazine, and 1,350 cc. of convalescent polio serum.

Comment

The external recti, last of the extraocular muscles to become paralytic, were also last to show any improvement. Convergence was early lost and not regained. Recovery from internal ophthalmoplegia was rapid. The seventh-nerve palsy occurred two weeks after onset of the illness, but recovery was more rapid than that of the third-, fourth-, or sixth-nerve palsies. Diplopia was an early symptom and extraocular-muscle involvement was prominent, well in advance of spinal-cord symptoms.

Summary

Although ocular complications of acute anterior poliomyelitis are not uncommon, ophthalmoplegia is rare. A case of bilateral complete ophthalmoplegia with left seventh-nerve palsy is presented.

606 North Brand Boulevard (3).

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METHOD FOR RESTORATION OF HUMAN ORBITS FOLLOWING NECROSCOPY ENUCLEATION*

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Detroit, Michigan

The field of keratoplasty and sight restoration is relatively new but in its short existence has attracted widespread interest. It is evident that the continued progress in this science depends, in a very great measure, upon the proficiency in obtaining eyes for pathologic study as well as for corneal transplantation.

It has been our experience while working with the Wayne University Eye-Bank, which was under the direction of Dr. Parker Heath, that the education of the public to give their eyes, at the time of death, depends to a large extent upon the assurance by the physician that the orbit will be restored to a normal outward appearance.

The object of this study is to present an approved, simplified technique for restoration of the human orbit. There will be no external evidence of alteration if the orbital cavity is prepared in accordance with the following procedure.

Material

Hemostat, cellulose cotton, sealer solution[1] ("Stix," Gold Crest Chemical Corporation,† 1063 Jackson Avenue, Long Island City, New York), eye caps (Edward S. Butler Company, 33 Otolaya Terrace, San Francisco, California), are the materials needed.

Procedure

The first step is to control the leakage from the terminal branches of the ophthalmic artery as they enter the orbit through the narrow apex of the muscle cone. This is accomplished by thoroughly crushing the tissue at the apex of the orbit with the aid of a hemostat. The optic nerve will also require crushing if it has been severed near the globe.

The capillary type of leakage is adequately controlled by sealer solution which is applied with cotton in a thin film over the orbital walls and permitted to dry. This is sufficient to seal the vessels and to withstand the usual pressure of injection of embalming solution.

The remainder of the orbital cavity is then filled with a cotton ball of suitable size followed by insertion of the eye cap.

(The author wishes to acknowledge suggestion and aid given him by the Department of Mortuary Science, Wayne University, Detroit.)

1512 St. Antoine Street (26).

* From the Department of Ophthalmology, Wayne University School of Medicine and the Receiving Hospital, Detroit.

† References are made to commercial manufactures for the sole purpose of giving information as to sources of supply of material. There is no intention of implying that other commercial sources are not equally satisfactory.

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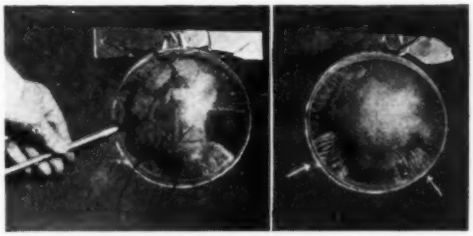
BLACKBOARD CORNEA FOR TEACHING

ANDREW DE ROETTH, SR., M.D.
Spokane, Washington

The teaching of clinical ophthalmology is rather handicapped by the small size of the eye. When not a few individuals but a whole class has to be instructed, the use of the blackboard, slides, or moving pictures is imperative. When pathologic conditions of the anterior segment have to be demonstrated on the blackboard, one is handicapped by trying to draw on a plane, that is in two dimensions, conditions which are three dimensional.

To overcome this difficulty, a blackboard cornea for teaching purposes was devised. This is a cornea made of plastic material.* The measurements are 15 times the size of a normal-sized cornea, except in thickness. This gives a horizontal diameter of (15 by 11.75 mm.) 17.6 cm., a radius of (15 by 7.7 mm.) 11.5 cm. The scleral overlapping at the upper and lower limbus is indicated by a frosted crescentic portion 12-mm. wide at the 12- and 6-o'clock positions. The thickness of the blackboard cornea is only 3 mm. instead of (15 by 1) 15 mm., to make it light.

When demonstrating a condition of the anterior segment of the eye, a circle is drawn around the border of the cornea while this is held against the blackboard. The cornea is then removed, and the iris and pupil and the pathologic condition under discussion are marked on the blackboard. The cornea is fastened against this drawing with a 3.75-cm. (1½-inch) wide piece of Scotch tape placed across its upper edge. This makes it possible to lift the cornea by its lower edge if further drawing is necessary in the iris plane or on the posterior surface of the cornea. Now the pathologic condition of the cornea can be marked. Grease pencils of different colors have to be used, because chalk does not write on plastic. These marks can be removed with warm water and soap, or more easily and faster with cleaning fluid (for example, energine) or plastic remover. The demonstration is more lifelike on a white board or frosted glass.



Figs. 1 and 2 (de Roetth, Sr.). Blackboard cornea. Fig. 1. Large central corneal scar with superficial vessels. Pencil pointing to a vessel. Optical coloboma of the iris between the 3- and 4-o'clock positions. Fig. 2. Interstitial keratitis with two bundles of deep vessels. Dull corneal reflex due to epithelial edema.

Figure 1 shows a central corneal scar with superficial vessels. There is an iris coloboma at the 3- to 4-o'clock positions and a sharply outlined corneal reflex.

Figure 2 demonstrates interstitial keratitis with very dull corneal reflex and two bunches of deep corneal vessels which were drawn on the posterior surface of the cornea.

The blackboard cornea facilitates the demonstration of pathologic conditions of the anterior segment. In addition to this cornea of plastic material, colored grease pencils, 1½-inch wide Scotch tape, and cleaning fluid (energine) to remove the markings are all that are needed to operate it.

Old National Bank Building (8).

* Plastic Modern Company, Spokane, Washington.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

COLORADO OPHTHALMOLOGICAL SOCIETY

December 21, 1946

DR. GEORGE STINE, *presiding*

LEONTIASIS OSSEA

DR. EDNA M. REYNOLDS presented Mrs. C. B., aged 52 years, as a case of leontiasis ossea which is limited to the sphenoid bone on the right side. The patient gave a history of a severe fall at about the age of six years in which the right side of her face was struck against a curbing. There was no apparent deformity until seven years ago when she hit the right eye on the knob of a chair in leaning over to pick up papers off the floor. After this injury, the right eye became prominent. In 1940, she went to Colorado General Hospital because she found that she could not see with the right eye.

When she was first seen in July, 1944, the right eye showed proptosis with limitation of movement laterally. Measurement with the exophthalmometer showed 28 mm. for right eye and 19 mm. for the left. (The same readings were found at Colorado General Hospital in 1940.) Vision was reduced to light perception.

The vision of the left eye without correction was 20/15+ and the eyeground was normal. An X-ray study of the skull was made by Dr. Harmon Brandenburg, who made the diagnosis of leontiasis ossea. The X-ray report was as follows: "Primary involvement of the sphenoid on the right side, with lamination of frontal bone; closure of the sphenoid fissure and foramina including the optic, causing blindness of the right eye and protusion of eyeball due to enlargement and pressure from behind."

Leontiasis ossea is the name given to the condition of hyperostosis of the facial and cranial bones. The disease has also been termed megalocephaly and hyperostosis of the skull. Since there was no tendency to malignancy, no treatment was advised. In these patients there is a tendency toward slow healing, and in this case, there had been no advance in the condition in a 4-year interval.

The patient was seen again in September, 1946. At that time, there was no apparent change in her condition and X-ray pictures showed no advance in the condition. Enucleation of the right eye for cosmetic purposes has been considered but declined by the patient.

CAVERNOUS OPTIC ATROPHY

DR. R. W. DANIELSON presented A.M.K., a 73-year-old clerk, who had come to the office about a month previuosly complaining of failing vision in both eyes of several years' standing. He had been to an optometrist recently who was unable to improve his vision. He had had no pain or other symptoms of glaucoma. On examination, uncorrected vision of the right eye was 20/100, and of the left eye, 20/15. This could not be improved with correction. The media and fundi were normal except that there was a deep cup in the temporal four fifths of each disc. The lamina cribrosa was not plainly visible. There was no overhanging of the edges of these cups. However, the appearance of these cups was such that one would offhand have certainly made a diagnosis of glaucoma. The perimetric field of vision with a 3-mm. white test

object showed only a small strip near the point of fixation on the 180-degree meridian of the right eye. In the left eye there was an almost concentric contraction down to about 20 degrees. The tension on each eye was 20 mm. Hg (Gradle-Schiøtz) and, after dilatation with homatropine for two hours, the tension was still 20 mm. Hg in each eye.

The patient was placed on pilocarpine. The next day the intraocular pressure was 13 mm. Hg in each eye. This pressure was taken on several subsequent days and was never found to be above 20 mm. Hg, except on one day following a provocative water-consumption test when the pressure of the right eye rose to 24 mm. Hg. On this day, pilocarpine had not been used, the water test was repeated using pilocarpine at the same time. In this instance, tension of the right eye did not increase after consumption of large amounts of water, but tension of the left eye went from 20 mm. Hg to 24 mm.

This appeared to be a case of so-called low-tension glaucoma until it was finally decided to make an X-ray study of the patient's sella turcica. Surprisingly, the X-ray report revealed changes in that region probably secondary to meningioma. The case was referred to Dr. Charles Freed, a neurosurgeon, who verified clinically the probability of an intrasellar tumor and recommended exploration.

Discussion. Dr. Freed discussed the case and gave a résumé of the clinical signs and symptoms of the various types of lesions that can occur in the sella-turcica region.

Dr. George Filmer told of a young woman patient who complained of slowly progressive blurring of vision. Peripheral fields were normal, although there were small central scotomas in each eye. Spinal fluid was normal. The case resembled early optic neuritis. She developed right homonymous diplopia and, during an exploratory craniotomy, a large cystic Rathke's pouch was found. The patient died. This cavernous atrophy of the disc very closely resembles glaucoma cupping, even to the overhanging veins.

Dr. T. Van Bergen asked if normal eyes gain in pressure after much water is imbibed in a short time. Dr. W. H. Crisp asked if local sclerosis could cause these changes. Dr. Freed added that any visual loss is an indication for surgery in these cases because this loss is irreparable; otherwise, X-ray therapy might be attempted. These explorations are not dangerous and should be done whenever reasonable doubt exists.

Dr. Danielson, in closing, said that changes in the normal eye probably do not occur after much water intake so that water imbibition serves as a good provocative test in glaucoma. Local sclerosis could resemble this case, but there now seemed no doubt that this was a case of cavernous atrophy.

Diabetic cataract

Dr. Ralph Jorgenson presented L.H., a boy, aged 18 years, who complained of sudden loss of vision over a period of three days about three months before. A general practitioner found him to be diabetic, and he was sent to Colorado General Hospital. Examination revealed bilateral, advanced, subcapsular cataracts with no fundus details visible. Blood-sugar level was 260 mg. percent, and urine sugar showed a 4+.

Disinsertion of retina

Dr. Ralph Jorgenson presented D.R., a 38-year-old man, who had noted that vision of his left eye was suddenly becoming poor about three months before. This decrease in vision had continued. There was no history of trauma. He was recently sent to Colorado General Hospital where examination revealed the

retina to be disinserted over the lower half at the ora serrata extending from the 4- to 7-o'clock positions. No tear was seen. Field studies showed absence of the superior half of the field except for a circle of about 10 degrees around the fixation area. Vision now is: R.E., 20/15; L.E., 20/70.

Morris Kaplan,
Secretary.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

December 2, 1946

DR. BENJAMIN FRIEDMAN, *president*

TECHNIQUE AND COMPLICATIONS OF KERATOPLASTY

DR. R. TOWNLEY PATON presented (with motion pictures) this subject. He stated that corneal transplantation, although not difficult for the experienced surgeon, should first be practiced on animal eyes. Over the years, experience has shown that the judgment needed in the selection of cases is learned only by those who have done many of these operations. Ideal cases for operation are relatively rare, and it is for this reason that it is best to have one eye surgeon do a lot of these cases rather than have many surgeons who perform only one or two keratoplasties a year.

The visual results in certain selected cases for operation are often dramatic. Postoperative complications increase in direct proportion to the size of the graft. Grafts of at least 6 mm. should be used in keratoconus cases, and only those cases in which there is a central corneal opacity or in which contact lenses cannot be tolerated should be operated upon. Postoperative complications in suitable cases are few. Many cases are operated, whose prognosis is bad to begin with. Our present knowledge has reached a point where we can select the operable cases with a fair degree of certainty.

Donor material. The eyes of newborn and premature infants are not satisfactory because the corneal tissue is more delicate and too malleable which causes more postoperative edema; also, these eyes do not keep as well.

Operative technique. Cutting the donor eye first gives the operator an opportunity to get the feel of his trephine. The trephine must be absolutely sharp.

The transplanting of corneal tissue for the treatment of scarred corneas has proved successful in many carefully selected cases. The operation itself is not of recent origin. Many cases were operated upon before 1900, but successful results have only been reported in recent times. Types of cases favorable for operation include those in which the scarring is central and not too dense and those in which no increased intraocular pressure is present. The presence of a large number of blood vessels in the cornea may often spoil the result of the operation. There must not be any active corneal disease present or any disease of the surrounding tissues. Uveitis of recent occurrence may be an exception.

Cases in which the scarring is limited to a small central area of the cornea, not over 5 mm. in width, and the scarred area is surrounded by healthy corneal tissue, entirely free of vessels, and the eye is otherwise considered to be normal give the best, and often the most startling, visual improvements. Visual improvement from 20/200 to 20/20 or better may be expected.

Keratoconus has not, in Dr. Paton's experience, given the best visual results for several reasons. He wished to report on only those cases in which the vision cannot be improved by means of glasses or contact lenses beyond 20/200. Because of

the dangers of using larger transplants, the operation is difficult.

NEW TYPE ORBITAL IMPLANT

DR. NORMAN L. CUTLER presented this subject with motion pictures. He stated that this implant for use in enucleations is composed of a plastic sphere with a gold ring for muscle attachment and a gold face plate into which fits a metal pin on the prosthesis. This gives a positive mechanical contact between the prosthesis and the implant.

An average movement of the prosthesis of 70 degrees, horizontally, and 65 degrees, vertically, is obtained. In addition, there is instantaneous movement over the shorter ranges. Some patients who can converge preoperatively are also able to converge postoperatively. The film showed postoperative results of this type of implant.

Discussion. Dr. Byron Smith said that past experience, with heterogeneous tissue transplantation and integumentary tolerance to foreign bodies justifiably causes us to accept with skepticism any advance in this field. In retrospect, it is difficult to understand why we have been so retarded in a more logical approach to the proper camouflage of ocular prostheses.

Nonirritating foreign bodies, completely submerged in tissues, are relatively well accepted by the human organism. Partially submerged foreign material as described by Drs. Ruedemann, Cutler, and Hughes, defies the laws of nature and has a tendency to nullify our previous concepts of surgical principles. The discouraging cosmetic results and complaints of the patients suffering from the presence of the early Ruedemann implant are not uncommon to some of us. The complex secondary surgery required in the removal of such an implant is, unfortunately, familiar to few ophthalmic surgeons.

At a meeting of the American Ophthalmological Society, in 1945, Dr. Wendell Hughes presented the details of a partially submerged vitallium integrated implant. He suggested that an oval, rather than a spherical, contour is an advantage in preventing rotation of the implant. Rounded rather than square corners at the contact between the implant and artificial eye was described as an asset in maintaining hygienic conditions in the orbit containing the prosthesis.

Erosion of glass by the fluids of the eye socket is frequently encountered. Individual allergy to plastics and plastic eyes is a recognized affliction. It is assumed that erosion and allergy of partially imbedded vitallium is less than might be expected from plastic.

Since I am not acquainted with Dr. Cutler's surgical resident, but have had an opportunity to observe Dr. Hughes, it is probably unfair for me to remark that implantation of the device into the muscle cone and Tenon's capsule is a major surgical undertaking. The modified Mules implant of vitallium described by Dr. Hughes for insertion through the sclera beneath the superior rectus muscle by the Burch technique of evisceration is technically simple and immediately effective. The narrow peripheral, perforated disc of remaining cornea securely surrounds the zenith of the implant, heals rapidly, and has been the source of no sensitivity.

In closing, I would like to ask Dr. Cutler a few questions:

1. What is the duration of time required for you to execute the implantation of the prosthesis you have initiated?

2. Have you encountered local tissue allergy to the implant in any of the cases you have treated?

3. Have you observed any postoperative deviation or rotations of the implant on its anterior-posterior, vertical or horizontal axis?

Dr. E. Waldstein asked whether it is necessary to use general anesthesia.

Dr. Barnard asked if the implants could be removed by the patient, and if so how frequently, and how difficult it would be to replace them.

Dr. Bernard Kronenberg asked whether it would be worth while to use the oblique muscle in this procedure.

Dr. B. Friedman asked if it were possible to reoperate old cases.

Dr. Cutler, in closing, replied that there are other techniques which are being used that are of interest. He remarked that since there is so much interest being shown at present in the use of implants, some day something adequate will be discovered for a heretofore inadequate procedure. He expressed the hope that there would be sufficient improvement to standardize the procedure in enucleation. The limitation of space in which a prosthesis has to move makes perfection impossible.

Dr. Cutler's procedure takes about one hour. It is rather tedious, but does not require anything unusual in experience and skill. The fact that these operations were done by eight different men in the first two dozen cases, indicates that it is quite routine. In regard to local allergies, he stated that he had not seen any local reaction from plastics. Some of the patients were observed for six months and none of them developed any tropia. Some of his patients have been seen by other ophthalmologists and no cases of tropia have been reported.

As regards doing the operation under general anesthesia, Dr. Cutler said that it could be done, but that he is inclined to use sodium pentothal on most middle-aged patients.

As for removing the eye and cleaning it, contact-lens suction discs have been used. The length of time it can be kept in the socket varies a great deal. Some individuals can leave it in for 1 or 2 months without removing it.

In regard to the oblique muscles, nothing has been done, since that would add quite a bit to the operative procedure. As for reoperating for removal of glass balls, one of these operations had been done and it is planned to take preoperative and postoperative motion pictures of some others. In these cases all that is done is to make a cruciate incision through the conjunctiva and roll Tenon's capsule around the ring and suture it into place. There is no particular advantage in isolating muscles. In this case the technique worked without difficulty.

Trap-door operation for glaucoma

Dr. Louis A. Lehrfeld spoke of Lieut. Col. H. Herbert of the Indian Medical Service, who had contributed many splendid articles on the surgical treatment of glaucoma from 1903 to 1934. Dr. Lehrfeld described (with motion pictures) the well-known "trap door" or flap operation, which had been devised by Dr. Herbert initially for absolute glaucoma but which was later used for all forms of primary glaucoma.

Using a narrow Graefe knife, an incision is made in the sclera, 2 mm. long and 1.5 mm. from the corneal margin in the lower outer quadrant of the globe. From the two ends of this small incision, two shorter forward cuts are made to the limbus by turning the edge of the same narrow blade forward and sawing carefully to avoid puncture of the iris. Thus, a small rectangular flap or tongue of corneoscleral tissue is made.

A modification of the technique is presented by making the trap-door in the silent or safe area of the sclera, in the region of the pars plana ciliaris. This site is selected, because there can be no damage to the ciliary, no damage to the lens, or no damage to the iris. Heretofore, all operations for primary glaucoma were in the region of the corneoscleral junction, the danger zone of the eye, where sur-

gery in itself may so complicate the glaucoma as to prove fatal to the eye.

Dr. Lehrfeld said that no attempt is being made to substitute the Herbert operation for the well-known and accepted surgical procedures for glaucoma. The modified Herbert operation is offered as an additional, elective surgical procedure, based on the principle of securing a continuous and slowly draining aperture in the sclera away from the danger zone and in the silent area of the eyeball.

Discussion. Dr. B. Friedman asked whether, in the event that the tension is not controlled by the operation, this would lead to a staphyloma of the operated area. Would leaving such a large opening in a vulnerable spot subject the eye to rupture from external pressure?

Dr. Lehrfeld, in closing, replied that in 20 cases which he had operated, no such occurrences had taken place.

Bernard Kronenberg,
Secretary.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

November 19, 1946

DR. HOWARD F. HILL, *presiding*

VISUAL ACUITY TESTED WITH MOVING OBJECTS

DR. ELEK J. LUDVIGH said that, in view of the absence of any information on this subject, it was deemed advisable to conduct an investigation of this subject, particularly since the eyes are so often and critically employed under these conditions.

The first and simplest type of motion to be investigated was that of simple rotatory motion of the test object. This was obtained by viewing variable sized Snellen test letters through a prism of various strengths rotated so that letters appeared to travel about in a circle in a plane perpendicular to the line of sight, monocular observation being used. Visual acuity was reduced by increasing the angular velocity and by the speed of the moving test object. The conclusion was that when an eye follows an object moving about in a circle in a plane perpendicular to the line of sight, the acuity will be reduced either by reason of the eye being unable to move sufficiently rapidly or by reason of the inability of the individual to change the innervation to the various eye muscles sufficiently rapidly, or both.

When the visual acuity was tested with the eye following an object moving in the horizontal dimension, an angular velocity of 170 per second was required to reduce the vision to 20/200, whereas when the test object was rotated, an angular velocity of only 62 per second was required. This was to be expected since experiments with the rotating test object showed that inability to change innervation rapidly was a factor and that conjugate lateral movement is apparently a relatively simple movement to innervate.

Dr. Ludvigh then outlined further proposed lines of investigation with the test object moving in various ways and conversely with the test object being stationary and nystagmus being present. In the latter situation initial experiments had been started by making short exposures of letters to see if the visual acuity was increased or decreased in a case of nystagmus, but conclusions could not be drawn. He said that he would welcome any further suggestions on this problem.

In the discussion that followed, the use of the stroboscope in the study of nystagmus was suggested, but Dr. Ludvigh thought that the swing of the nystagmus was not sufficiently regular to employ it. In reply to questions in regard to head movements, Dr. Ludvigh said that they had not been permitted in the experiments as yet because it would be superimposing

another factor on the problem of eye movements. However, he thought that the fixation in following moving objects would be more accurate with head movements permitted, inasmuch as the head would take care of the grosser portions of the movements, which would necessitate the eyes following only a little.

Problem of ophthalmic education

Dr. W. J. B. Riddell of the University of Glasgow, Scotland, gave the main paper of the evening. He said that in recent years great thought and planning have been devoted to various aspects of medical education. Certain factors have contributed towards this activity in the United States and in Britain. There has been a desire on the part of the Universities and Medical Schools to raise the standard of the undergraduate course, and this has led to a demand for more trained graduate instructors. This activity has been more marked in America where the ratio of teachers to students is very high compared to Europe. Facilities for study in other medical schools and the provision of necessary scholarships, free from routine clinical work, have increased the interest aroused in graduate training. The number of such opportunities is many times greater in America than in Britain.

The medical courses in the two countries differ in important respects. The British student graduates as a Bachelor of Medicine and Bachelor of Surgery (M.B., Ch.B.) from his University after a course lasting five or six years; a certain proportion, around 15 to 20 percent, proceed to the higher degree of Doctor of Medicine (M.D.). It is not possible to obtain the latter degree without possession of the two former ones. The graduate wishing to specialize, particularly if he aspires to a position on the staff of a teaching hospital, must also obtain a Fellowship from one of the Royal Corporations. These corporations are medieval guilds which have continued throughout the centuries in a modified form.

It is possible to obtain a Fellowship in which ophthalmology forms part of the examination in Scotland and Ireland. New regulations for the English Fellowship are projected in which ophthalmology forms the principal subject of the final examination. A primary examination on the basic series of Anatomy, Physiology, and Pathology will remain common to all candidates.

The diploma in Ophthalmic Medicine and Surgery (D.O.M.S.) is obtained by examination and is of somewhat similar scope to the certificate of the American Board of Ophthalmology. It was introduced mainly to raise the general standard of ophthalmic practice and to assist the public, insurance societies, and similar bodies in recognizing medical men qualified to carry out ophthalmic examinations.

One of the dangers attending the elaboration of highly trained specialists is that there tends to be an excess of experts in certain chosen centers who are unwilling to leave the academic or scientific atmosphere in which they have been reared. In so far as this happens it is a reflection upon the teachers; they have failed to produce an all round craftsman capable of performing his chosen job of work apart from elaborate equipment and buildings. There is no doubt that a great loneliness descends upon the young surgeon during the years immediately following his period of residence and research in a big center. This lasts until he finds his feet in a new area, but the isolation may be relieved by the stimulating effect of small visiting surgical clubs and associations. Organizations of this type were dear to the heart of Osler, whom it will be recalled started at one time to become an ophthalmic surgeon. Our loss has been the great gain of general medicine, and

we may speculate upon what he would have contributed to ophthalmology had he devoted his genius to it.

There are certain developments in ophthalmic teaching which can be regarded with some misgiving. Many students have to spend time on acquiring an examination knowledge of subjects in which they have no real interest and no practical acquaintance. Some planners seem unable to appreciate a vital educational principle which was expressed so clearly by Sir Richard Livingstone, Master of New College, Oxford, a few years ago. "The principle is that almost any subject is studied with much more interest and intelligence by those who know something of its subject matter than by those who do not; and, conversely, that it is not profitable to study theory without some practical experience of the facts to which it relates."

Dr. Riddell has great hope and confidence that ophthalmology will continue to develop powerfully in both England and America. In Britain they envy our libraries, clinics, and research facilities; they are proud of their own clinical traditions and are conscious of their scientific failings. In no special branch of medicine is a sense of historical perspective so well developed as in ophthalmology. The great British clinical school of the 19th century was followed by the dominant position gained by Germany at the beginning of the century. Britain now turns towards the New World for inspiration and finds it in full measure.

Discussion. Dr. Edwin Dunphy said that an English friend once said to him (and Dr. Riddell touched upon it tonight): "The greatest bar to misunderstanding between our two countries is our common tongue."

In continuing, Dr. Dunphy said that because of the fact that we speak the same language, many of us on either side of the Atlantic might feel that we should have the same customs. As a matter of fact, they differ tremendously in many respects. I am sure that Professor Riddell has been just as mystified by many of our medical customs as I was with the British system when I lived there in 1943 and 1944.

Professor Riddell has outlined some of the similarities and differences as they appear to him. As an American living in the British Isles, one of the things that impressed me most was the absence of the State Board examinations.

Another notable difference that impressed me was the extremely young age at which the British medical men can begin to practice. There are no age requirements for matriculation in the medical school, a man will often enter at the age of 17 or 18 years, and will graduate at the age of 22 or 23 years. Practically 15 or 20 percent of these men have an A.B. degree.

Although such a system lightens the economic burden, it would perhaps seem to us that the advantage must be weighed against a certain lack of maturity in starting to heal the sick, and also, possibly, a lack of training in the liberal arts. That might seem so, but, as a matter of fact, the difference is not as much as you would think, because I am quite sure that the average young Briton, aged 17 years, is much more matured than the American of the same age.

Coming to ophthalmology—both Britain and America are faced with the problem of not having enough ophthalmologists. I think that is true in this country more than in Britain. That is, we need ophthalmologists to take care of all the ophthalmic needs of the population.

For instance, in the United States, as you all know, 75 percent of the refractions of the general population are done by optometrists. Some may not think that is a very bad thing, and others think it is too bad. Also here in this country, we

have 7000 ophthalmologists, and we need, as was said, about 300 new ones a year to make up for the loss in death and retirements. We were training, as of December, 1941, 180 new men and women a year, and now we are qualifying about 250 a year. Therefore, we have a deficiency in the residency training of ophthalmologists. Certain other candidates are being trained by means of short courses and apprenticeships, and are being certified by the American Board of Ophthalmology, if they pass the necessary examinations. The American Board has not reduced the standards of the examinations, and, as far as I know, does not intend to.

In order to meet this shortage problem, we can either develop more residencies to train more men to become top-flight surgical ophthalmologists, or else we can train more medical ophthalmologists by means of postgraduate courses. If we adopt the former plan, and if it were possible to double or triple our residencies, we would have to cut down on the amounts of surgery and on the individual instruction of surgery, and there would not be enough to go around. On the other hand, if we greatly expand our postgraduate system courses to take in hundreds and hundreds of new men, we may be able to develop enough medical ophthalmologists to become good sound diagnosticians who can compete with the optometrists in serving the refraction needs of the country, leaving the residency training to the men who do the surgery.

In an editorial, I read some comments upon the difference between the American and British outlook in this teaching program: "The aim of the American side of the Atlantic is a very thorough and complete training of a relatively few high-grade specialists. On the British side, the aim and basic conviction of a large number is for a shorter time, leaving it to the initiative of the few to obtain for themselves the final gloss and polish of academic distinction."

The American Board of Ophthalmology stated that short courses are an abomination, unsound pedagogically, and productive of a poor grade of practitioners. Nevertheless, Lancaster feels that we should be realistic about the situation, and face the fact that there never will be enough residencies to take care of the demand. Therefore, he feels that perhaps it is better to give short basic courses to all who apply, trusting that enough good men will be given their chance to make good and go ahead to make up for the undoubtedly great number of poor men that will be taken in. He feels that these basic subjects can be taught by lectures, quizzes, and reading, and thus large groups can be instructed at one time. Those who cannot obtain residencies should be placed as apprentices in older doctors' offices. How such a scheme will work remains to be seen. I think it is too soon to judge it.

Here at Harvard Medical School, we feel that laboratory work is essential to the teaching of basic sciences. This type of teaching can best be done with relatively small groups and by full-time research men rather than clinicians. This basic training should be followed by clinical residencies, with a form of instruction continued by clinical men. This is the policy that we are maintaining. I admit that it doesn't solve the main problem in the slightest. Perhaps the solution may lie in the development of ophthalmic technicians such as has been suggested by Parker Heath, who is with us tonight. Such a group could be developed in the colleges—not right away, of course, but on a long time program—giving about two years of training in physics, chemistry, biology, physiology, mathematics, and optics. This two-year training period would be followed by perhaps a one year

training in the hospitals, in refractions, and so forth. Such a person could then be employed by the ophthalmologist and work entirely under his supervision. Perhaps such an ophthalmologist could employ two, three, or four, and the load would be correspondingly reduced.

I don't know the answer to the problem. I do not for a moment doubt the sincerity of purpose of those who believe in training large numbers and in so-called medical ophthalmologist short courses. Personally, I mistrust the wisdom of such a course. A number of men so trained by this course will undoubtedly develop into very excellent ophthalmologists, I know, but I fear that we may flood the country with some very mediocre material.

Dr. Parker Heath said that he was very much interested in the various angles which had been discussed. Since ophthalmic technique was a little hobby of his, he was glad to say something about it.

The point is that optometry itself is a dying profession. There were relatively few going into optometry before the war, and the present increase in optometry is apparently a by-product of the educational impulse which is going around the country.

Ophthalmology has not met the needs and qualifications, so far as the demands are concerned in the medical field. We have had this tried and true method of training people whereby every doctor had a nurse or someone else trained to help him with the onerous part of the practice. The extent to which these assistants can go is dependent on the ability to teach of the man in the office. That is, the assistant can do refractions, assist on smears and cultures, assist in the office and have a real, not quasi, professional relationship which can be described as an ophthalmic associationship. The basic principle involved is the distribution of medical care. The public isn't accurate in its classification of teachers and practitioners. Only by roundabout methods do they find out where to go and what to do about their optic difficulties. So, the boards are established to help in this matter—State boards, ophthalmic boards, and so on.

The problem is one of medical care and medical distribution of this care. Any thing we can do to help shift the care and cover a wider field is going to help solve the problem.

I put forth this idea, which isn't necessarily mine (it might be an old idea in a new dress) of the ophthalmic associate —one who serves under medical aegis all the way through, who is bound by the same medical standards maintained under the same medical code, not answerable to a board outside but under medical ethics to the American Board of Ophthalmology.

We seem to be living a one standard or preaching a one standard practice, but at the same time to be living a two standard existence, because there are medical ophthalmologists and surgical ophthalmologists, and the greatest need is for medical ophthalmologists. I would say why not have two kinds of diplomas? This would be one solution, so these people who are medical ophthalmologists can have their place in the sun and be a recognized group. They prefer their work to that of the surgical ophthalmologists.

The second suggestion is to furnish a group of ophthalmic associates who can be educated in colleges as far as humanities are concerned. Technical training can be given by medical men themselves.

Dr. S. Judd Beach said that the first thing that he had to say was in regard to the course that Dr. Lancaster has supervised and organized. If Dr. Lancaster were here to speak for himself, Dr. Beach felt sure that he would agree entirely with Dr. Dunphy that the thing to aim for is the type of course given at Harvard rather than the short courses which have been arranged to fill in during the in-

terval when nothing else is available. A course is obviously better when it is conducted along didactic lines, followed by a proper laboratory and clinical program. The type of course that Lancaster has arranged cannot fairly be called a short course, in the sense that the refresher courses, for instance, are short. There are short courses at the George Washington University and in Rochester, but they are entirely different.

Concerning the men who have come up to the Board for examinations the records of those taking the study council courses have been, I won't say all that is to be desired by any means, but very much better than those of the men who have taken a refresher course, feeling that it would fit them for a Board examination.

Dr. Beach expressed to Dr. Riddell the indebtedness of the Board for making the suggestions which led to the formation of the Board. These suggestions came through Dr. Jackson and were based on the type of examinations which were given in Britain. In the second place, Dr. Lancaster's course was copied in some part from the courses given at Oxford, which Dr. Riddell has mentioned tonight and which he had a part in organizing.

In the third place, Dr. Beach thought that the very important suggestion which Dr. Riddell had made ought to be considered, and that was that medical ophthalmology should be perhaps more thoroughly worked out in the examinations by, as he said, neurologists and the like for examiners. Actually we should have a second surgical certificate from the Board, to be given to those men who can do surgery. Dr. Beach said that the young men who come into our office tell him that they find it very much more difficult to perform good refractions than operations. He is not at all sure but that the second and advanced certificate should be given in medical ophthalmology.

DR. RIDDELL (in closing): You have mentioned how easy it is for a medical man to practice in Britain, that he needs only register to protect the public. That is nothing—any layman can operate with a razor blade if he wishes to. If the patient dies, that is too bad. If he is a registered medico, he's O. K. Similarly, a quack cannot sue for fees. Apart from that, it is a free country.

You also mentioned that students start earlier. The average age is 18.3 years. As for myself, I skipped off to the Navy. They start in the University with biology and physics.

In regard to refractions—it is the same in Britain as in America, 75 percent are done by the optometrists and opticians.

A great deal of the training is done by apprenticeships and bedside teaching. That's one of the reasons why the universities in Britain are opposed to technical training—they are not keen on building up technical training in the universities. For some reason, there are no professors, or hardly any specialized professors in the universities. That's just the way we do things.

This business of ophthalmic technique is a very difficult one. We will probably do something similar to what Dr. Heath outlined for you tonight. I wouldn't be surprised if we were to have supervised ophthalmic technicians for Scotland.

Medical ophthalmology is an enormous thing in itself. It can be very fascinating. There have been surgeons who have abandoned the surgical in order to devote all their time to ophthalmology. There is a larger question of proportion in these things that has to be considered. That is how I think about it—we must have technical assistants (call them optometrists) in an equal proportion or balance for the particular community or state which has to be served.

AMERICAN JOURNAL OF OPHTHALMOLOGY

Published Monthly by the Ophthalmic Publishing Company

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OPTOMETRY AND OPTICAL DEVELOPMENTS

In his testimony before the Committee on Military Affairs, House of Representatives, held in Washington on July 3, 1945, at a hearing on a bill to establish an optometry corps in the Medical Department of the United States Army, Mr. Leslie R. Burdette of Salem, Oregon, past president of the American Optometric Association, included the following remark in his statement: "Parenthetically, I should like to add that these highly developed instruments which are so necessary for the correct diagnosis of visual defects have in most instances been invented or considerably improved by physicists and optometrists not by physicians." In refuting this claim, Dr. Alan C. Woods, professor of ophthalmology, Johns Hopkins University School of Medicine, stated: "They (the optome-

trists) have made extraordinary claims regarding the apparatus that they have designed and perfected. In answer to that claim, I can only tell you that in the Wilmer Institute, which I believe is one of the best equipped in the world, I do not know of one single, solitary piece of apparatus in the whole institution that owes its genesis to optometry."

Legalized optometry is only 39 years old, dating from 1908 when the first optometry law was passed by the State of New York. It was instigated by Charles F. Prentice so that he could legally charge a fee for his services. Like the creator of Frankenstein, the father of optometry found that his brain child developed otherwise than he would have wished, and in his memoirs decried the unwarranted assumption of the title "doctor," pseudoscientific pretenses, aggressive commercialism, and dubious practices.

At the same time that optometry made its advent, ophthalmology had reached a high degree of development, especially in the field of physiologic optics and optical instruments. The progress through the ages had first been very slow, and to the mathematicians we owe the fundamental laws of optics—Euclid, Alhazen, Snell, Gauss, Euler, Listing, and Lambert. The astronomers—Galileo, Airy, Kepler, and Hooke—gave us the telescope and the spherocylindrical lens, clearer conceptions of the function of the human eye and vision, and the concept of the minimum separable. The learned clergy-scientists—Roger Bacon, Sheiner, Mariotte—contributed the first publication on spectacles, the demonstration of accommodation, and the knowledge of the blindspot. The physicists—Newton, Fraunhofer, Brewster, and Wheatstone—discovered the nature of color and invented the stereoscope. The physiologists and psychologists—Mueller, Weber, Koenig, von Kries and Weber—clarified the facts of visual sensation and adaptation, giving interpretive significance to the data of anatomy, histology, and biochemistry. Much of this, and particularly the pioneer works of Young and Helmholtz, paved the way for the monumental work of Donders that appeared in 1864 and at last placed refraction of the eye on a scientific basis. On this firm foundation, numerous ophthalmologists have contributed to the superstructure—notably Tscherning, Nagel, and Duane. The problems of orthoptics and ocular motility, first emphasized by Javal, numbered among its eminent devotees Stevens, Savage, Howe, and Maddox.

Meanwhile the optical armamentarium rapidly increased. In 1784, Benjamin Franklin invented bifocals; in 1804, Wollaston designed the meniscus lens; in 1839, photography was simultaneously discovered by Daguerre and Talbot; in 1851, came Helmholtz's epochal ophthalmoscope. In 1857, Jaeger provided reading charts; and in 1862 Snellen devised the modern refraction chart. In 1867, Green introduced the improved astigmatic dial, modified by Lancaster and Verhoeff, now used. Cuignet invented the retinoscope in 1874; Javal and Schiøtz, the ophthalmometer in 1880. Of the numerous optical instruments since developed and in daily office use, none of which, parenthetically, have been devised by optometrists, probably the most essential are Jackson's cross cylinder, Gullstrand's slit-lamp and corneal microscope, and Lloyd's stereoscopic scotometer.

The optical companies with their scientific staffs in applied optics have made and are making notable contributions. Von Rohr popularized vertex refraction and punktal lenses; Clifford Brown furnished the valuable duochrome test; and worthy improvements in bifocals have been made available.

The history of the development of contact lenses is liberally coated with

the names of physicists from Sir John Herschel, 1845, to Müller, 1887, and Professor Abbe of Carl Zeiss, 1888. Fick, ophthalmologist of Zürich, in 1888, coined the term "contact lens." Dallos of Budapest made the first impressions of the eye with negocoll, followed later on by Obrig, an optician. With much fanfare, Feinbloom, an optometrist, and Beacher, an optometrist, hopped onto the band wagon. There is now a considerable commercial value in the business of fitting contact lenses.

The authors of the leading textbooks that are used in the schools of optometry —Southall, Sheard, Fincham, Emsley, Swaine—although teaching in schools of optometry are not optometrists at all, but are physicists specializing in the applied optics of refraction.

The writings by the practicing optometrists in the various journals of optometry are quite another story. Here we see glasses with invisible tint, cures for color blindness, the improvement of vision without glasses à la Bates, muscle and prism exercises for the cure of myopia, revolving colored lights for the cure of many ocular diseases, unknown and unnamed, expensive nonsense for remedial reading, and visual training couched in gobbledegook language. All of these practices betray an ignorance or disdain of the fundamentals of physiologic optics, anatomy, physiology, and pathology of the human eye. Could it be possible that Mr. Burdette, O.D., was referring to these items in his remarks about "highly developed instruments?" If so, then the ophthalmologist will gracefully concede him the honors.

Derrick Vail.

OPHTHALMIC DISPENSING

Perhaps "optical dispensing" would be a rather more logical term; but there may be a certain utility in recognizing that the great State of New York has adopted the caption title in its dealings with the subject. The implications of either term are sufficiently broad to touch the whole optical trade, even indirectly the wholesale manufacturer of lenses, although more particularly the frame maker and dealer, the retail optician, some jewelers, the refracting optician or optometrist, and the prescription optician. Many physicians who dispense their own prescriptions would come within the heading, although exempt from special laws dealing with this practice.

The ophthalmologist who relies upon the work of retail opticians rather than upon his own personal activities in optical dispensing learns to have considerable confidence in the judgment and, as suggested by Post in his editorial in the June issue of this JOURNAL, even the advice of such opticians as to technical details concerning frames and lenses. But the ophthalmologist may also find cause to be disgusted at the inadequacy of training of other optical technicians with whose work he comes into occasional contact.

It is a source of satisfaction to know that there exists within the ranks of the optical trade an active movement toward improvement in the standards of optical dispensing. Ophthalmologists who realize the importance of the subject may profitably study the April-May issue of *Guildcraft*, the organ of the Guild of Prescription Opticians of America (1947, volume 20, number 6).

Among other items, that issue contains the following material. First, the New York State Department of Education announces its initial Examination in Ophthalmic Dispensing, held May 8 and 9, 1947, under the special provisions of the Education Law adopted by the State of New York in 1946. This law requires that ophthalmic dispensers practicing as

such on July 1, 1947, must hold certificates in that capacity issued by the Department of Education, unless duly licensed to practice medicine or optometry in the State. Subject to certain exceptions as to those already engaged in such practice, candidates must have completed a year of study in a "school of ophthalmic dispensing registered by the Department as maintaining a satisfactory standard," or must have had at least one year of acceptable training and experience in ophthalmic dispensing under the supervision of an ophthalmic dispenser, physician, or optometrist.

The next item in the quoted issue of *Guildcraft* describes a technical course offered by the Institute of Applied Arts and Sciences of the New York State Department of Education, including periods in mathematics and physics; in "ophthalmic materials" (including the history of spectacles, development of ophthalmic lenses, the manufacture of lenses, and various details with regard to glass, grinding and polishing materials, metals, alloys, and plastics used in the optical trade); in prescription laboratory technique; in lens surfacing; and in the verification and inspection of spectacle products. Further, the student is instructed in the principles of refraction and the phenomenon and theory of vision and the physics of light; including the principles involved in various well-known ophthalmic instruments. Finally, he is given a definition and outline of "services rendered by each group in the eye-care field."

The fourth item in the April-May issue of *Guildcraft* is the noteworthy address by Benedict, mentioned in Post's excellent editorial in the June, 1947, issue of the *American Journal of Ophthalmology* (page 765). It will have been observed from that editorial that the Junior College of Rochester, Minnesota, on the initiative of the Ophthalmological Division of the Mayo Clinic and of four major trade organizations, has already created a two-year course in "Opticianry" (a new term coined for this purpose), and that it is proposed to follow that course by at least a five-year apprenticeship before the candidate is permitted to apply for certification as "Master Ophthalmic Optician."

No doubt opportunity will be afforded later to compare this plan with that announced from New York, and indeed with other such educational schemes which may be expected to develop in different parts of the United States. It will be interesting to consider how such plans are likely to influence the development of shop and counter work in optics, as well as the trade and professional relations between ophthalmologists, optometrists, and the general public.

When, in 1827, the astronomer Airy calculated the strongly compound myopic astigmatic error of his own left eye, with its "major axis" at 35 degrees from the vertical, he went to an Ipswich optician named Fuller, who ground the necessary concave spherical curvature on one side and the concave cylindrical on the other.

Fuller no doubt was a man of moderate schooling but of long apprenticeship to a master optician. In those days it was the common thing for technical training to be obtained by many years of apprenticeship. The apprentice first ran errands, fetched materials, delivered finished work, cleaned out the workshop and guarded it in his master's absence, and was gradually, and in the course of time, intrusted with the execution of mechanical details, so that he became more or less thoroughly intimate with the principles and practice of the artisan to whom he had been bound by contract.

The same sort of approach to expertness was found in the studio of the sculp-

tor or painter artist or in the printing establishment. The teaching of medicine or of the "apothecary's art" long went through somewhat similar developments, and it is only something like three quarters of a century since the great majority of this country's physicians depended, at least for a large part of their training, upon the guidance of a preceptor to whom they occupied a relation somewhat similar to that of the apprentice in other crafts.

A comparable approach to the optician's craft may be found today in opticians' stores and workshops. However, there is bound to be a variation in the extent to which the modern optician concentrates either on the craft of making lenses or on the commerce of selling them to the public. More and more the nonacademic approach to any field of activity is recognized as open to the criticism that it leaves gaps in the pupil's knowledge. The counter optician may have had little to do with the actual grinding of lenses. On the other hand he must himself be a craftsman of a sort in the fitting of spectacle frames and also in checking the accuracy of the shopman's work. As in most lines of mechanical activity, it is pretty certain that some individuals will know more about one aspect of the craft or trade, others more about other aspects; and that few will be equally adept or learned in all details.

In such wide variations of individual experience, training, and skill lies a sound basis for demanding standardization in the technical education of those who minister to the public's optical needs. Many of those engaged in the optical trade have scattered their energies over too wide a field of related but more or less distinct responsibilities. They attempt to be at the same time diagnosticians, mechanics, and salesmen. It is well to remember that the Guild of Prescription Opticians itself represents a healthy tendency toward concentration on the dispensing of optical goods.

To what extent will the general public gain by the movement now fostered, in somewhat different shape, on the one hand by the New York Board of Education and on the other hand by the Mayo Clinic in coördination with a group of optical organizations? The type of training at first selected by those who, after passing through high school or college, decide to establish themselves in one branch or other of the optical trade, will depend partly, as now, on financial considerations, and partly on the miscellany of circumstances which make for choice of job or career among the general population. Some will start without vision or ambition for the future and will develop plans as they go along. In this feverish age, perhaps not many young tradesmen will be induced to plan for a two-year course of training which may, after a further five-year apprenticeship, lead to certification as Master Ophthalmic Optician. It may be suggested that such a certificate would have to compete with that of "Doctor of Optometry," a title which is the professional goal of many of today's optical dispensers.

Granted that a move for educational standardization in this practical line is desirable, it is likely that many such as now enter the retail optical trade in a rather casual fashion will continue to do so, and that of these at least a fair proportion will still seek to obtain a state license to practice optometry.

Whereas the New York Department of Education has decided to call the trade "Ophthalmic Dispensing" (which for practical purposes we may consider as identical with "Optical Dispensing") and another group of educators, including Dr. William L. Benedict and Charles Sheard, Ph.D., propose to call it "Opticianry," may it not be better to adhere to a single

title, and of the two titles to use that which is the more adequate and logical? The term used by the New York State Board of Education appears to cover the subject rather well (unless "Optical Dispensing" is preferred) and to be logical in form, whereas the entirely new term "Opticianry" is of somewhat dubious etymology and vague significance. The two may of course persist side by side. What's in a name?

W. H. Crisp.

BOOK REVIEWS

KERATOPLASTY AND TISSUE THERAPY. By V. P. Filatov. Moscow, State publications of medical literature, 1945. 232 pages. 233 illustrations.

This book, by the chief of the Ukranian Experimental Institute of Ophthalmology, best known for his pioneer work in keratoplasty and for his recent development of a new method of therapy with preserved animal and plant tissues and their extracts, gathers in a monograph the formerly published data of the Institute, and adds the material accumulated during the war in the various military hospitals. When the Institute in Odessa was abandoned because of the Nazi invasion, the staff of the Institute was assigned to various military hospitals where the doctors had an opportunity to pursue their clinical studies. In 1942, the Institute was reopened in Tashkent.

The preface to the volume is as revealing as some of the technical expositions. As his catechism of faith, Filatov declares that only optimism and therapeutic activity can lead to progress. He believes that every organism holds hidden within it potentialities for recovery, if one could but release them. One must therefore never give up the exploration of therapeutic resources, and when forced to admit defeat, one must leave the patient with a hope and expectation of some new discovery, which may bring relief. "Pessimism at the bedside and in science is fruitless, and not to it belongs the future." This philosophic attitude helps to understand what otherwise, because of the skepticism incident to accurate scientific evaluation, might appear as an unrestrained flight of an unscientific imagination.

The volume actually consists of two monographs, which Filatov combines for the purpose of historical perspective, inasmuch as tissue therapy was the outgrowth of his experience with keratoplasty. The first part, dealing with keratoplasty, reviews in detail the clinical experience based on about 1,000 cases, and the experimental and research data in connection with it. Filatov introduced the use of cadaver cornea into keratoplasty, and through the study of eyes enucleated after successful transplantations, demonstrated that the transplant forms a true union with the cornea of the host, and is not merely a scaffold for the ingrowth of corneal elements from the recipient's cornea. It was also shown that the cornea is preserved best without fluids at a temperature of 3°C.; under these conditions the oxidative processes are continued in the cornea and lens; and despite autolysis the preserved cornea continues to exhibit cellular division and growth. The descriptions of the indications, the various techniques, and the instrumentation conform to the requirements of a good textbook, and 143 satisfactory photographs demonstrate the final results.

In the part dealing with tissue and tissue-extract therapy, Filatov explains in detail the hypothesis which he elaborated, with some support from known biologic and botanical phenomena, to explain the rationale of this new form of therapy which is hailed in a tone of evangelism.

The numerous reports which appeared on this subject from the Ukraine Institute during the last five years had many of us wondering about the pharmacodynamics of what seemed to be advocated as a universal panacea. The fact that there were no reports on this subject from other Russian ophthalmological institutions, makes it probable that Filatov also met the normal scientific skepticism in Russia. This book is a detailed exposition of the motivation, the underlying hypothesis, the experimental data, the clinical studies, and the technique on the subject.

Preserved tissue and tissue-extract therapy is a nonspecific form of therapy, the therapeutic agent being designated as biogenic stimulators, or resistance substances, the existence of which is assumed, and the chemical nature of which is still in the process of investigation, the probability being that they are amines. They develop as a result of biochemical reconstruction in all living tissues and plants in response to an unfavorable environment, which harasses life but does not extinguish it entirely. They in turn stimulate biologic processes, and it is believed that such a phenomenon takes part in the process of evolution. Animal or plant tissues isolated from their organism, and subjected to an unfavorable, but not mortal, environment also undergo biochemical changes, resulting in the production of these substances. Tissues rich in these substances, introduced into another organism, become stimulants of the physiologic functions of the host.

In disease, pathogenic products inhibit the production of substances necessary for regenerative processes; and, on the other hand, the same pathologic process after reaching a certain intensity and duration initiates the development of biogenic stimulants; the crisis of acute infectious diseases is interpreted as the indication of a spurt in their appearance. The introduction into a sick organism of tissues rich in biogenic stimulants augments its cellular metabolism, and counteracts the inhibiting effect of pathogenic products on the formation of substances necessary for recovery. The unfavorable environment giving impetus to the formation of biogenic stimulators comprises variations in temperature and light, and various chemical agents. This in substance is the theory on which this form of therapy is based. Filatov believes that this type of therapy is in its inception, and that there are many problems yet to be cleared up.

How can maximum action of these substances be obtained? How can they be isolated? There are problems of sterility and stability; there is the possibility of specific stimulants. This, he says, is too big a task for a single investigator and he seeks to interest other workers. The techniques for the preparation of the various preserved homologous, heterogenous, and plant tissues and extracts, and their therapeutic application are described in detail, in the hope that this information will lead to their wider use. Filatov foresees that the hypothesis may not stand the test of future investigations, and may be substituted by another theory based on a more factual foundation. Extensive clinical research may limit the sphere of usefulness of this form of therapy. But, whatever the explanation, he believes that the therapeutic effect of preserved tissue has been demonstrated and will remain incontrovertible.

The clinical material subjected to this type of therapy consists chiefly of hopeless cases, discharged as such from other ophthalmologic institutions. It is not difficult to understand that in such cases even very slight improvement may lead to an exaggerated enthusiasm. During the war the effectiveness of this therapy appears to have been confirmed in the various military hospitals, principally in Mid Asia,

where Filatov and his students worked. Regardless of the fate which the future holds for this form of therapy, the patience and the deep human sympathy motivating the sustained and prolonged efforts to restore to practically blind people a semblance of vision, adequate perhaps only to enable them to get about unaided, command our respect. The language barrier will make Filatov's book inaccessible to most ophthalmologists, and it is hoped that this review will at least define the pattern of his work.

Ray K. Daily.

RESEARCHES ON NORMAL AND DEFECTIVE COLOUR VISION. By W. D. Wright, A.R.C.S., D.Sc., with a foreword by L. C. Martin, D.Sc., A.R.C.S., D.I.C., St. Louis, C. V. Mosby Co., 1947. Clothbound, 383 pages, 233 illustrations. Price, $10.00.

This volume is the last word on experimentation and theory of color vision. It is the result of some 20 years of research. L. C. Martin, professor of Technical Optics in the Imperial College of Science and Technology, London, states, in the foreword, that the fundamental problems of color vision are still unsolved. The author writes: "This book should be regarded first and foremost as a record of experimental data, with theoretical discussion and speculation occupying a very secondary position." He goes on to express his personal belief that the three-response theory along lines proposed by Young and Helmholtz is probably correct. He does not, however, wish to ally himself too strongly with any theory as he believes that much work remains to be done. His opinion is that many exact experiments, the suggestions for which have already been made, should be performed as an aid toward establishing incontrovertible theory.

The first 40 pages are devoted to the anatomy of the visual organ and the physiology of visual perception. Each succeeding chapter is introduced by a paragraph or two outlining the work contained in that chapter and in some cases descriptions of instruments that were used in the experimental work.

Most attention is devoted to the trichromatic system which is discussed exhaustively. If the mathematical details are passed over briefly by the average reader, much of practical interest to him will be found. Obviously the mathematics and other details are vital to the deeply interested student of color vision and to such a person the book is invaluable. It also will serve as a good reference book of the most recent researches in this field.

Lawrence T. Post

CORRESPONDENCE

Editor,
American Journal of Ophthalmology:

In the April, 1947, issue of the JOURNAL (page 491), Dr. S. Rodman Irvine reported on the January meeting of the Research Study Club of Los Angeles. In his report on my presentation of the subject of retinal detachment, he stated that I felt that about 10 percent of the detachments have a hole in the macula area that needs treating. This is a serious misunderstanding which, I feel, should be cleared up. I feel that probably one percent, or at most two percent, of detachments have a hole in the macula. I feel that many operations for a hole in the macula have been done when there was no hole present. I would appreciate it very much if this statement could be published to correct the impression created by Dr. Irvine's excellent résumé of the Los Angeles meeting.

(Signed) Dohrmann K. Pischel,
San Francisco, California.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below, which broadly correspond to those formerly used in the Ophthalmic Year Book. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. General methods of diagnosis
2. Therapeutics and operations
3. Physiologic optics, refraction, and color vision
4. Ocular movements
5. Conjunctiva
6. Cornea and sclera
7. Uveal tract, sympathetic disease, and aqueous humor
8. Glaucoma and ocular tension
9. Crystalline lens
10. Retina and vitreous
11. Optic nerve and toxic amblyopias
12. Visual tracts and centers
13. Eyeball and orbit
14. Eyelids and lacrimal apparatus
15. Tumors
16. Injuries
17. Systemic diseases and parasites
18. Hygiene, sociology, education, and history
19. Anatomy, embryology, and comparative ophthalmology

RETINA AND VITREOUS

Cristini, G. **Retinal spongioblastoma.** Rassegna Ital. d'Ottal., July 1943-Dec. 1945, v. 12-14, pp. 450-467.

The author reviews the various phases of the development of our knowledge of the pathology of retinal tumors from the time of Virchow in 1869. The different classifications proposed by numerous investigators are presented. He describes a retinoblastoma observed in a 28-months-old child, which extended outside the globe, along the optic nerve and the vorticose veins. Histologically there were two distinct areas, one portion showing spongioblasts which were highly anaplastic, and the other astroblastic. It would appear, therefore, that neoplasms may arise in the retina which are analogous to those which develop in the encephalon. (10 figures.)

Eugene M. Blake.

Cutler, N. L. **Vitreous transplantation.** Trans. Amer. Acad. Ophth., 1947, March-April, pp. 253-259.

The vitreous contains about 99 percent water yet has a viscosity 20 to 200 times higher than water. It is a solgel in an unstable state, subject to syneresis under various conditions.

The results of 13 vitreous transplants, of which eight were done for vitreous hemorrhage and five for retinal detachment, are summarized. Of the former four were considered successful and one partially successful; of the latter, one was successful. In eyes with hemorrhage, the vision improved from light perception to 20/50 and from 20/200 to 20/25. All the operated patients previously had normal light perception and tension.

Following sodium pentothal anesthesia and scleral exposure, a 2-mm. incision is made through the sclera with a Graefe knife. Mattress scleral sutures are then placed and 1.5 cc. of vitreous is withdrawn with a syringe and 18 gauge needle. The barrel is disconnected but the needle is left in place. A syringe barrel containing 2 cc. of clear vitreous from a freshly enucleated eye is attached to the original needle and

injected into the vitreous. The sutures are tied, atropine instilled, and a binocular dressing is applied.

Chas. A. Bahn.

Friedenwald, J. S. **Disease processes versus disease picture in interpretation of retinal vascular lesions.** Arch. of Ophth., 1947, v. 37, April, pp. 403-427.

This article constitutes the Sanford R. Gifford Memorial Lecture of February 18, 1946. The four major, potentially independent, processes of vascular disease include senescence, atherosclerosis, the hypertensive arteriolosclerotic process and diabetic vascular disease. These processes are discussed in detail with special reference to the pathological changes involved. The comprehensiveness of this important article makes it unsuitable for condensation. John C. Long.

Fritz, M. H. **The substitution of cerebrospinal fluid for vitreous clouded with opacities.** Amer. Jour. Ophth., 1947, v. 30, August, pp. 979-984. (12 references.)

Gördüren, Süreyya. **A Grönblad-Strandberg syndrome.** Brit. Jour. Ophth., 1947, v. 31, April, pp. 228-232.

The author discusses the literature and presents an interesting case of Grönblad-Strandberg syndrome, with the two components of the disease, angioid streaks and pseudo-xanthoma elasticum, clearly demonstrated. Angioid streaks, which are due to the widespread degeneration of elastic tissue, were present in both eyes. A large, yellow, raised mass was present in the posterior pole of one eye. The skin of the neck and abdomen had a parchment-like appearance with raised yellow streaks. Microscopic examination of the skin in biopsy showed degeneration of the elastic elements. (7 illustrations.) D. H. Ellis.

Guyton, J. S., and Reese, A. B. **The use of X-ray therapy for retinal diseases characterized by new-formed blood vessels.** Trans. Amer. Acad. Ophth., 1947, May-June, pp. 525-546.

In 14 patients 22 eyes were treated during 18 months with intensive X-ray therapy for vascular diseases of the posterior part of the eyeball. The doses ranged from 400 to 500 r three times weekly and were administered principally temporally. Eight patients had typical Eales disease, 4 had atypical Eales disease, and 2 had diabetic retinitis proliferans. Shrinking of the smaller vessels was observed two to three weeks after therapy and disappearance from ophthalmoscopic visibility occurred in 4 to 8 weeks. If the total dosage did not exceed 4,000 r the larger new-formed vessel showed partial shrinkage, but if more than 10,000 r the larger vessels disappeared. Regression of fibrous tissue was marked only with 10,000 r. In typical Eales disease hemorrhagic recurrence was observed but once. X-ray therapy was of no apparent value in diabetic retinoses. The marked friability of new-formed retinal vessels facilitates proliferative processes. X-ray therapy primarily affects new-formed blood vessels in the retina and vitreous. The total dosages used were 3,500-15,000 r per eye, the optimal dosage 6,000 r.

In the discussion, Alvaro reviewed the X-ray treatment of hemorrhagic retinal disease which dates back to 1919. Opinions concerning its efficiency vary widely. The effect of X-rays upon blood vessels is discussed in detail. In retinitis proliferans, the new formed blood vessels represent an effort to re-establish blood flow in an area of im-

paired circulation. Doses as small as 50 r repeated every five days have been advised. Larger doses are advised if blood vessels have formed at the disc and entered the vitreous. Hard rays are advisable in retinal therapy.

Blood in the vitreous is frequently absorbed more readily after therapy in doses of 300-1300 r. Hemorrhages in diabetic retinopathies are best treated with small doses, though the proliferative vascular process is not appreciably affected. Retinal thrombosis and occlusion of the central vessels with hemorrhage are not altered by X-ray therapy. (22 figures, 10 in color.)

Chas. A. Bahn.

Iglesias, F. G. **Etiology and treatment of recurrent vitreous hemorrhages in the young.** Arch. de la Soc. Oft. Hisp.-Amer., 1947, v. 7, Feb., pp. 139-162.

A comprehensive review of the literature is presented. Ray K. Daily.

Kinney, T. D., and Fitzgerald, P. J. **Lindau-von Hippel disease with hemangioblastoma of the spinal cord and syringomyelia.** Arch. Path., 1947, v. 43, May, pp. 439-455.

The authors present two cases of Lindau-von Hippel disease.

Irwin E. Gaynon.

Klein, B. A. **Angioid streaks.** Amer. Jour. Ophth., 1947, v. 30, August, pp. 955-968. (10 figures, 14 references.)

Matteucci, P. **Contribution to the treatment of central retinal vein thrombosis.** Rassegna Ital. d'Ottal., July 1943-Dec. 1945, v. 12-14, pp. 394-404.

Three cases of retinal vein thrombosis are reported with satisfactory results from treatment with retrobulbar injections of alcohol. One cc. of 2-percent novocain is first injected, and after an interval of five minutes one cc. of 70-percent alcohol is introduced. The treatment is repeated in a week if necessary. The good results are ascribed to a transitory hypotension of the globe accompanied by a dilation of orbital, retinal, and uveal vessels. A similar reaction is found in experimental animals. The treatment is recommended in painful glaucoma that is hemorrhagic, absolute, or secondary to iridocyclitis. Eugene M. Blake.

Scuderi, Giuseppe. **The effect of adrenalin, ephedrine and simpamina upon arterial retinal pressure.** Rassegna Ital. d'Ottal., 1947, v. 16, Jan.-Feb., pp. 3-40.

Adrenalin and ephedrine injected subcutaneously in doses of 1 mg. and 5 ctg. respectively, lower the retinal arterial pressure, especially the diastolic. This is probably due to a passive, compensatory hyperemia. Simpamina (betaphenylisopropalamina sulfate) on the contrary, in doses of 20 to 40 mg. produces a constant elevation of the pressure, whereas 10 mg. has only a negligable effect upon the diastolic pressure. The author suggests that the retinal arteries are capable of less contractility, and thus are less sensitive than other vascular regions of the body. (3 tables, 39 references.) E. M. Blake.

Silfverskiöld, R. P. **Retinal periphlebitis associated with paraplegia.** Arch. Neurol. and Phychiat., 1947, v. 57, March, pp. 351-357.

The author describes three cases of a remarkable syndrome. The patients, young men of about 30 years of age, first exhibited characteristic retinal periphlebitis with recurrent hemorrhages in the vitreous. After varying

intervals of time, only four to six weeks in two cases, the ocular disease was followed by subacute paraplegia, with considerable pleocytosis. During the follow-up period of one to two years the patients were observed to show improvement in varying degrees.

An investigation showed that a combination of retinal periphlebitis and neurologic disease is rare.

Theodore M. Shapira.

Stine, G. H. **Detachment of the choroid and the retina. Anatomic and other considerations in the differential diagnosis.** Amer. Jour. Ophth., 1947, v. 30, July, pp. 897-906. (1 table, 3 figures, 22 references.)

Taylor, Charles. **A Case of the Laurence-Moon-Biedl syndrome showing atypical retinitis pigmentosa associated with macular dystrophy.** Brit. Jour. Ophth., 1947, v. 31, April, pp. 211-215.

A case report of Laurence-Moon-Biedl syndrome is presented which shows the rarely-seen combination of atypical retinitis pigmentosa and macular dystrophy. The retina showed scattered pigment, and the macula was spotted with pigment. The vision was poor. The "bone corpuscle" pigmentation was not predominant. The author points out the interesting fact that analyses of reported families of this condition revealed a large number of miscarriages and early deaths, indicating severe disturbances in the genes.

O. H. Ellis.

Weinstein, P., and Forgács, J. **Circulatory studies of the fundus of the eye.** Brit. Jour. Ophth., 1947, v. 31, April, pp. 238-242.

According to the authors, patients with spontaneous venous pulsation of the fundus blood vessels have a better retinal circulation and show 50 percent less retinal complications than persons without pulsation. In patients with pulsation the pressure drop from the arterial to the venous circulation is greater; without pulsation the arterial pressure is established at a higher level signifying capillary obstruction. Spontaneous venous pulsation disappears with reduction of intraocular tension by massage of the globe.

O. H. Ellis.

11

OPTIC NERVE AND TOXIC AMBLYOPIAS

Casari, G. F. **Alveolar meningioma of the optic nerve sheath.** Rassegna Ital. d'Ottal., 1947, v. 16, March-April, pp. 137-148.

The tumor described appeared in a 39-year-old man. The first symptom was epiphora, soon followed by progressive exophthalmos of the left eye. The interest in the tumor arises from its rarity and from its location. It had developed in the sheath of the nerve just posterior to the optic foramen. Usually the process starts in the intraorbital portion of the nerve. The cytologic picture of the tumor is fully described. The author discusses the development of tumors of the sheath, the nerve, and those of the sheath and the nerve. (4 figures.) Engene M. Blake.

Lian, S. B. **Camp amblyopia.** Ophthalmologica, 1947, v. 113, Jan., pp. 38-44.

During the Japanese occupation of Java (1942-1945), the author saw many cases of an eye condition which he had never seen before and which the Dutch physicians assigned to the concentration camps had named "camp amblyopia." The condition occurred in

white males who had been put into concentration camps where improper and bad food prevailed. The patients' chief complaint was inability to read. Ophthalmologic examination revealed reduced central visual acuity, central scotomas, normal eye grounds (except for small striate retinal hemorrhages in a few patients) and no gross systemic abnormalities. Toward the end of the Japanese occupation when the food situation had become worse, the author saw the same condition among free (uninterned) civilians, first in the clinics for the indigent and later in his private practice. After a review of the literature pertaining to this and similar conditions (which had occurred in China, Japan and certain parts of Africa long before the last war), Lian reports five cases of camp amblyopia in patients who showed remarkable improvement after the addition of vitamin B_1 to their otherwise unchanged diet. Although favorable results were obtained with thiamin chloride alone, the author thinks that camp amblyopia is not simply a deficiency of Vitamin B_1. None of the patients with camp amblyopia showed any signs of beri-beri which still is the outstanding vitamin-B_1 deficiency disease. On the other hand, in true beri-beri, optic nerve involvement is rare. Also, it seems significant that camp amblyopia did not occur in concentration camps in Holland and Germany where the food situation was as bad as in the Dutch East Indies. Therefore the author suggests that camp amblyopia is not entirely due to a B_1 deficiency but rather to a complex deficiency in which lack of protein and minerals is an important factor. The problem of camp amblyopia is rather complicated, and there is much further work to be done.

Peter C. Kronfeld.

12

VISUAL TRACTS AND CENTERS

Kravitz, Daniel. **Arachnoiditis.** Arch. of Ophth., 1947, v. 37, Feb., pp. 199-210.

Arachnoiditis is an inflammation of the leptomininges which may be localized or diffuse, even to the extent of involving the entire central nervous system. Infection, especially of the paranasal sinuses is the commonest cause. Syphilis, trauma, and otitis are other important causes. The symptoms may vary considerably depending on the location, extent and severity of the lesion. Headache is frequent. In the opticochiasmal form, sight is frequently jeopardized and the discs are rarely normal. There may be primary, secondary, or segmental atrophy of the nerve, or even extreme degrees of choked disc. At times arachnoiditis may simulate cerebral tumor so closely that the true pathologic process is not revealed until operation is performed. At times the optic nerve is severely damaged by sharing in the same inflammatory process that produced the arachnoiditis. The most satisfactory treatment of arachnoiditis is the surgical separation of arachnoidal adhesions.

Nine cases of arachnoiditis treated surgically are reported.

John C. Long.

Lyle, D. J. **Diagnosis of visual losses with normal fundus.** Ohio St. M. J., 1947, v. 43, June, pp. 620-621.

Advanced arteriosclerosis and encephalopathies may produce visual loss without changing the normal appearance of the fundus. Affections of the retrobulbar optic nerves, chiasm, and optic tracts frequently do not produce changes in the fundus at first. The diagnosis is made by visual field studies, the reaction of the pupils, the

extraocular muscles, the trigeminal and facial nerves and other neurologic studies. Roentgenologic and other diagnostic aids should be used.

Vascular lesions most frequently are the cause of disturbance in the optic radiations. Tumors may cause visual hallucinations before they produce papilledema especially if present on the dominant side. The visual field defects from lesions in the radiations usually show sharp and congruous edges with sparing of the macular fibers.

The calcarine branch of the posterior cerebral artery is most frequently involved in lesions of the visual cortex. Vascular lesions frequently produce a large defect immediately, whereas lesions caused by expanding tumors become larger late and cause sector and indentation defects in the visual field. Visual illusions result from irritation to the psychic visual cortex chiefly from drugs, poisons, and toxins. Destruction of the para- or peri- striate areas cause a loss of visual perception, recognition, and revisualization.

H. C. Weinberg.

Monnier, M., and Jeanneret, R. L. **Objective recording of the conduction process in the visual pathway by combined electroretinography and electroencephalography.** Ophthalmologica, 1947, v. 113, Jan., pp. 1-11.

An interesting neurophysiologic study from the department of physiology of the University of Zurich is presented. Under conditions of complete sensory and mental rest, the electroencephalogram shows oscillations of a certain frequency and intensity which have been designated as alpha rhythm. Sensory stimulation characteristically inhibits or arrests the alpha rhythm (réaction d'arrêt, arrest reaction). This phenomenon of inhibition of a cortical activity by a sensory stimulus promises to permit closer study of the functional status of the visual pathway. Bertrand, Delay and Guillain in their monograph on electroencephalography (Masson & Cie, Paris, 1939) mention a patient with right-sided homonymous hemianopsia and aphasia whose alpha rhythm remained undisturbed by visual stimuli if the lead (for the electroencephalogram) was taken from the left occipital region. If the lead was taken from the right occipital region, typical alpha rhythm was obtained which was typically inhibited by visual stimuli. The authors (Bertrand, Delay and Guillain) attribute the ineffectiveness of visual stimuli upon the alpha rhythm emitted by the left occipital lobe to the obviously existing interruption of the left suprageniculate pathway.

The authors of the paper under review have studied the latent period of the arrest reaction (the so-called blocking time), in the hope that it would prove to be a finer, "more differentiated" criterion of the functional status of the visual pathway than the mere fact of presence or absence of the arrest reaction. The blocking time is determined in human subjects by combining electroencephalography with electroretinography. The examinee is seated before a perimeter on the arc of which the apparatus that provides the visual stimulus is mounted. The latter consists of a standardized light source, a projection system and colored filters. The leads for the electroretinogram are taken from the conjunctival cul-de-sac and from the temporal region, those for the electroencephalogram from the occipital region and from the lobule of the ear. Cathode oscillographs are used to record the variation in potential. After the alpha rhythm has been obtained and recorded for a few seconds,

a visual stimulus is applied. It causes (1) a subjective sensation, (2) the various phases of the electroretinogram and (3) inhibition of the alpha rhythm of the electroencephalogram. The blocking time, that is the time from the inception of the light stimulus to the very beginning of the inhibition of the alpha rhythm, has been found to be 0.169 second (for a normal subject under conditions of foveal stimulation). The simultaneously taken electroretinogram permits determination of the retinal portion of the blocking time, that is the time from the onset of the visual stimulation to the moment the impulses are discharged into the optic nerve. This retinal portion or retinal time has been measured to be 0.045 second (under the conditions stated above). By deducting this retinal portion from the total blocking time the postretinal or central time is obtained (0.124 second) which corresponds to the conduction time of the impulses within the visual pathway. In a patient with tabetic optic atrophy the postretinal time was found to be considerably longer and more variable than in the normal. Combination of electroencephalography and electroretinography promises to be a valuable method for the study of normal and abnormal conduction in the visual pathway.

Peter C. Kronfeld.

Verdaguer, J., and Olivares, M. L. **Parinaud's mesencephalic paralysis.** Arch. Chilenos de Oft., 1946, v. 2, July-Oct., pp. 226-234.

The patient, a man aged 33 years, came complaining of almost continuous occipital headache, dizziness, and uncertain gait. Examination showed incomplete paralysis of associate movements of elevation, incomplete paralysis of convergence, and Argyll Robertson pupil. Ventriculography had not yet been done, but the diagnostic impression was of a tumor of the quadrigeminal region. (References.)

W. H. Crisp.

13

EYEBALL AND ORBIT

Delsors, José, and Matheu Climent, J. **Fracture of the optic canal.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, June, pp. 536-543.

The authors report a case of skull fracture with involvement of the optic canal. A series of good X-ray pictures is presented to show the fracture that involves the optic canal. (7 illustrations.)

J. Wesley McKinney.

English, P. B. **Calcification occurring in the eye.** M. J. Australia, 1947, May 3, pp. 549-551.

Calcification may take place in the tarsal plate in chronic trachoma and in the conjunctiva in vernal catarrh and erysipelas. In the cornea it may be primary or may be secondary to hyaline degeneration. It is common at the optic disc and ora serrata and it also occurs in the sclera between the fibrils. The author reports a case in which the sclera, lens and vitreous were the seat of calcification after a postinflammatory fibrosis. (References.)

Irwin E. Gaynon.

Givner, I., Bruger, M., and Lowenstein, O., **Exophthalmos and associated ocular disturbances in hyperthyroidism.** Arch. of Ophth., 1947, v. 37, Feb., pp. 211-219.

In 21 of 22 patients with hyperthyroidism, pupillographic examination revealed a re-dilation block. This is believed to be hypothalamic in origin and lends the first tangible evidence to the confirmation of Marine's hypothesis

that exophthalmos is due to a stimulation of the hypothalamic centers which in turn stimulates the pituitary to produce the thyrotropic hormone, which in turn stimulates the thyroid gland, and, independently, the sympathetic centers in the midbrain, causing exophthalmos.

The administration of neostigmin bromide, a preparation of vitamin E and pyrodixine failed to reduce exophthalmos. Ergotamine tartrate temporarily and substantially reduced exophthalmos. The administration of iodine orally, and pregnancy may occasionally result in regression of exophthalmos.

If vision is impaired because of involvement of the optic nerve in patients with thyrotropic exophthalmos, complete uncapping of the optic foramen should be included in the Naffziger decompression. John C. Long.

Kennedy, R. J. **Ocular hemorrhages.** Cleveland Clin. Quart., 1947, v. 17, July, pp. 176-180.

Subconjunctival hemorrhage may result from trauma, compression of the chest, scurvy, or purpura. Vitreous hemorrhage occurs from trauma, arteriosclerosis or retinal inflammation. Retinitis proliferans is a serious sequel of vitreous hemorrhage. Occlusion of the central retinal artery causes a sudden loss of sight with the "cherry-red spot" at the macula. Hemorrhages may be small at the disc. Occlusion of the central retinal vein may be complete with a gradual loss of vision. The veins are dilated and the retina is covered with superficial and deep hemorrhages.

Hemorrhages in the uveal tract occur in arteriosclerosis, in iritis, and in the blood diseases. Choroidal hemorrhages produce permanent visual defects.

The vascular retinopathies are characterized by hemorrhage and exudate in addition to sclerosis, hypertension and toxemia. The striate and flame shaped hemorrhages are superficial in the retina whereas the round and irregular ones are in the deep layers of the retina. (2 figures.)

H. C. Weinberg.

Magitot, A. **The implantation of dead tissues in ophthalmology.** Ann. d'Ocul., 1947, v. 180, March, pp. 146-149.

Dead tissues used as implants in the orbit have one advantage over live tissues; they are absorbed less rapidly. Foreign substances, if similar embryologically, are usually well tolerated by the host. If cartilage is used the perichondrium should be removed. Cartilage preserved in formalin and alcohol, makes an excellent implant because it is easily vascularized and encysted. The author prefers the head of the femur of a dog that weighs about 15 Kg. It may be preserved in alcohol or formalin or sterilized in the autoclave and preserved in a sealed glass tube. Expulsion of tissue implants is less frequent than of inert substances such as metals or plastics. Implants should be covered by the ocular muscles, Tenon's capsule, and the conjunctiva. There is a moderate edema for four or five days and the implant is firmly fixed at the end of a week. The unsightly fold in the upper lid which is not infrequent after enucleation may be remedied by a cartilage implant.

The nerves in tissue implants do not survive. Corneal transplants from horses usually remain transparent in rabbits. Transplanted glandular epithelial implants such as the ductless glands frequently remain viable and in some cases functional. In successful corneal transplants keratoblasts from the host progressively replace those in the implant. Chas. A. Bahn.

Somerville-Large, L. B. **Panophthalmitis in a premature infant treated by streptomycin.** Brit. Jour. Ophth., 1947, v. 31, June, pp. 362-366.

A case of panophthalmitis in an 11-day-old, premature infant is reported. Pure cultures of bacillus proteus were obtained from the umbilical cord and the anterior chamber. The infection proved resistant to combined sulfadiazine and penicillin. It responded to streptomycin although not in time to prevent perforation and evisceration. Negative cultures were obtained from the excised uveal tissue which demonstrated the intraocular permeation of the streptomycin. O. H. Ellis.

14

EYELIDS AND LACRIMAL APPARATUS

Alvarez y Alvarez, Abundio. **Plastic surgery of the lids.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, Nov., pp. 1163-1173.

Imre's technique of plastic surgery of the lids is described. The author has obtained good results by using this method with some variation of his own, in which he uses sliding triangular flaps with curved borders and horizontal bases. (4 illustrations.)

J. Wesley McKinney.

Baclesse, F., and Ennuyer, A. **Indications for contact radiotherapy in the treatment of oculopalpebral tumors.** Arch. d'Opht., 1947, v. 7, no. 1, pp. 5-17.

The authors have treated more than 200 tumors of the external eye and lids in the past four years, of which 150 were epitheliomas of the lids, 2 were epitheliomas of the cornea, 2 were conjunctival lymphomas, and 25 were palpebral angiomas. The technic of so-called "contact radiotherapy" consists in the use of low voltage (50-60 K V), short focus (2-5 cm.), and minimal filtration. Its purpose is to give the first few millimeters of the lesion the maximum dosage while sparing the subjacent tissues. The authors consider it unnecessary to shield the globe when employing this technic and they have encountered no late unfavorable effects. They feel that their results have been exceptionally good.

Phillips Thygeson.

Barraquer Burch, Manuel. **A contribution to dacryocystorhinostomy.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, Nov., pp. 1150-1160.

With little change in the customary technique the author successfully performed 29 dacryocystorhinostomies. In suturing the anterior flap he only put two interrupted silk sutures through the skin, nasal mucosa, lacrimal sac and back through the skin again. The stitches are tightened over a small piece of gauze which can be very easily removed. (10 illustrations.)

J. Wesley McKinney.

Bock, R. H. **A simple modification of operations for entropion of the eyelids.** Arch. of Ophth., 1947, v. 37, May, pp. 650-651.

The method described makes use of the principle of the Hotz operation, namely, to fix the margin of the lid to the upper border of the tarsus by sutures. This, however, is done without cutting the skin, but only by passing three or four double-armed sutures from the conjunctival side through the upper border of the tarsus, then along the anterior surface of the tarsus downward and finally emerging through the skin 1 to 2 mm. above the row of eyelashes. The other end of the silk suture is passed in the same way about 2 mm. away from the first one, and the two

are tied on the skin side over a glass pearl on a small gauze roll after exerting the necessary pull to produce the desired correction. (1 figure.)

R. W. Danielson.

Carreras Durán, B. **A contribution to dacryocystorhinostomy.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, Nov., pp. 1132-1137.

To prevent injury to the nasal mucosa while trephining the bone in dacryocystorhinostomy, the author advises an injection (1 or 1.5 cc.) of 3-percent novocaine in oil, placed under the nasal mucosa at the site of the perforation. This will separate the membrane from the bone and prevent injury of the mucosa. He describes a simple syringe to be used for the injection. (2 illustrations.) J. Wesley McKinney.

Carrearas Durán, B. **Rare disturbances after Toti's operation.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, June, pp. 553-557.

A rare complication following a dacryocystorhinostomy is reported. The patient noticed a temporary change in her voice that lasted a few days two months after the operation.

J. Wesley McKinney.

Casero, L. **Inverse Bell's phenomenon.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, June, pp. 588-592.

In the normal Bell's phenomenon there is elevation and slight outward deviation of the eyeball when the lids are closed and in the inverse phenomenon the deviation of the eyeball is down and inward. A boy, 16 years old, with an inverse Bell's phenomenon is reported. The patient had suffered a traumatic wound on his right upper lid six years before examination. After this was healed there was an ectropion of the lid with conjunctival hypertrophy and an inverse Bell's phenomenon of the right eye. The abnormality is an acquired abnormality of oculomotor synergy. J. Wesley McKinney.

Chavarria López, F. A. **Large polyp of the right lacrimal sac with spontaneous healing.** Arch. de la Soc. Oft., Hisp.-Amer., 1946, v. 6, Nov., pp. 1127-1131.

The polyp developed in a patient who formerly had bilateral dacryocystitis, and at the time that he presented himself for examination had an acute attack of dacryocystitis of the right side. The polyp separated itself from the sac after spontaneous healing of the process.

J. Wesley McKinney.

Cornalba, Gaetano. **A case of cylindroma of the lacrymal gland.** Rassegna Ital. d'Ottal., 1947, v. 16, Jan.-Feb., pp. 41-49.

A 29-year-old man developed gradual exophthalmos and displacement of the left globe. The histologic picture showed the morphologic characteristics of a cylindroma of the orbit, originating in the lacrymal gland. The tumor consisted of mixed epithelial and endothelial cells with participation of fibroblastic tissue. (7 figures, 21 references.)

Eugene M. Blake.

Fox, S. A. **Lipiodol studies of chronic dacryocystitis.** Amer. Jour. Ophth., 1947, v. 30, July, pp. 878-884. (9 figures, 10 references.)

Landau, J. **A case of congenital vertical shortness of the lids combined with tetrastichiasis.** Brit. Jour. Ophth., 1947, v. 31, April, pp. 219-222.

The author reviews the literature, and presents an unusual case of congenital vertical shortness of the lids. The patient also had tetrastichiasis, combined with a partial eversion of the cutaneous part of the upper lid margin. It appeared that the hair follicles of the supernumerary cilia had taken the place of the Meibomian glands, and occupied their ducts. No inflammation of the eyes had occurred. O. H. Ellis.

Leriche, Rene. **Surgical treatment of Sjögren's syndrome; the result, after 28 months, of bilateral section of the vertebral nerve.** La Press Medicale, 1947, no. 7, Feb. 1, pp. 77-78.

Leriche reports the case of a woman 50 years of age who consulted him because of dry mouth and dry eyes of 12 years duration. Her general health was good except for menopause which had taken place during the course of her disease. The eyes showed complete absence of tears as measured with filter paper. Repeated sympathetic blocks with procaine each time produced a hyperemia of the facial region with lessening of the dryness of the mucous membrane. The roots of the vertical nerve on the right side were cut and a substellar segment of the cervical sympathetic chain which included the intermediate ganglion, was excised. There was immediate improvement subjectively and objectively. Five days later section of the roots of the vertebral nerve on the left side resulted in definite return of tears and subjectively the patient was much improved. The postoperative course was interesting in that the moisture in the mouth was maintained and the patient was able to shed tears for the first time in many years. The patient died 28 months later after a hemorrhagic purpura. Her husband stated that at the time of his wife's death she had still not obtained a true salivation but that her mouth was always sufficiently moist.

The author considers that surgical intervention is justifiable in a condition in which ordinary therapy is useless. He believes that the atrophy of the salivary and lacrimal glands may result in part from vascular failure and that surgical therapy leads to an active hypermia of these glands. The latter would be expected to increase their function.

In discussing surgical technique he considers it unjustifiable to remove the stellate ganglion because of the subsequent interference with the function of the heart-regulating mechanism and of the vasoconstrictors of the upper arms. The stellar ablation of the second and third dorsal ganglia would have the advantage of not producing Horner's syndrome. He states that his procedure of sectioning the vertebral nerve roots on the two sides is not the ideal operation since it leads to circulatory changes that are more cerebral than facial. It might be advisable to attack the middle part of the cervical chain, from the middle ganglion to the lower pole of the superior ganglion.

In discussing the pathogenesis of Sjögren's syndrome, Leriche considers the possibility that the disease may originate in a vasomotor disturbance that leads to elective atrophy of the glands. Phillips Thygeson.

Marin Amat, M. **Importance of the deep suture in dacryocystorhinostomy.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, Nov., pp. 1138-1149.

The author believes that success in dacryocystorhinostomy depends on the deep suture placed in the lacrimal sac

and nasal mucosa. He describes his own technique.

J. Wesley McKinney.

Rostkowski, L. **The operations of Hotz-Anagnastakis, of Denig, and of canthoplasty as performed in the anti-trachoma teaching organization.** Arch. d'Opht., 1946, v. 6, no. 4, pp. 456-459. (See Section 5, Conjunctiva.)

Selinger, Elias. **Tear sac probed through canaliculus of everted upper lid.** Amer. Jour. Ophth., 1947, v. 30, July, pp. 910-911. (2 figures.)

Sherman, A. E. **Reconstruction of the eyelid.** Trans. Amer. Acad. Ophth., 1947, May-June, pp. 514-524.

Three to four hundred patients with severe lid injuries were observed in nine Army General Hospitals during two years. Generally speaking, eyelid tissues should be replaced by eyelid tissues. The Wheeler technique which employs a full thickness graft carefully sutured in a previously prepared bed with excision of scar tissues is preferred. A good pressure dressing is considered important and should not be changed for five or six days. For small full-thickness losses and for vertical scars Wheeler's "halving" technique is advised. In younger patients the Hughes method of lid reconstruction is considered superior to Wheeler's sliding flap correction. If possible, avoidance of pedicle flaps from the forehead and cheek is advised. The Hughes method of total lower lid reconstruction is preferred if the tarsal part of the lid is missing. In extensive losses, the skin and subcutaneous tissue are elevated and with the conjunctiva are joined to the upper tarsus at a second operation. Bone grafts from the crest of the ilium may be used if necessary. Eyelash grafts are best taken from the middle portion of the nasal end of the eyebrow. Total reconstruction of the upper lid is not as satisfactory as that of the lower. Three illustrative cases are presented showing the use of full-thickness grafts. Two cases illustrate the "halving" operation; two cases, the total reconstruction of the tarsal portion of the lids by the Hughes method; and three cases, the Hughes method of lid reconstruction combined with other procedures. Chas. A. Bahn.

15

TUMORS

Costi, C., and Larru, E. **Treatment of ocular neoplasms by means of Chaoul's roentgenotherapy.** Arch. de la Soc. Oft. Hisp-Amer., 1946, v. 6, Nov., pp. 1175-1188.

The authors report in detail six cases of ocular neoplasm successfully treated by means of Chaoul's roentgenotherapy. They compare their results with those obtained in treatment of ocular neoplasms by other methods such as surgery, Xray, electrocoagulation, and radium and find that the highest percentage of success follows treatment by means of Chaoul's method. (11 illustrations.) J. Wesley McKinney.

16

INJURIES

Casanovas, José. **Double perforation of the eyeball in accident work.** Arch. de la Soc. Oft. Hisp.-Amer., 1946, v. 6, June, pp. 523-535.

Of 73,750 patients with ocular traumatism, 98 had a perforated wound with an intraocular foreign body. In 13 cases of double perforation of the

eye the foreign body was found to be within the orbit. The last 13 cases are reported in detail. (8 illustrations.)

J. Wesley McKinney.

Desvignes, P., and Boudon, C. **Statistical study of 418 penetrating injuries of the globe treated at the ophthalmological clinic of the Hotel-Dieu, from 1940 to 1945.** Arch. d'Opht., 1947, v. 7, no. 1, pp. 28-50.

The authors note the increase in the number of penetrating wounds as compared to the 394 cases reported by Dollfus and Halbron for the same hospital for the years 1925 to 1933. They explain this increase in part as a result of war injuries and in part as a result of the closing of other hospitals during the war years. Young adults were most commonly involved and of the 399 unilateral cases 322 were in males. There were 19 bilateral injuries, all but one of which were war injuries. Cause of the injury was known in 337 cases and of these 87 were industrial accidents with penetrating metallic foreign bodies; in 26 cases the penetrating agent was wooden. There were 72 infants in the series.

Prognosis varied according to the nature of the traumatism and the site of the wound and the authors give tables illustrating the end results of the various injuries. The percentage of retained globes with useful vision varied from 2.4 percent in the case of mutilating injuries to as high as 55.2 percent in the case of injuries by nonretained metallic agents. The extent of the injury had more prognostic significance than the site. There were no instances of sympathetic ophthalmia observed in spite of the fact that in 78 cases there was persistent uveal tract inflammation.

The authors conclude that the sulfonamides did not prove to be of striking value in preventing infection and that the prognosis of perforating injuries of the globe has not improved materially over the past 40 years in spite of advances in chemotherapy and improvement in surgical technic.

Phillips Thygeson.

Ershkovich, I. G. **Tissue therapy of sequelae of ocular war injuries.** Oftal. Jour. (Odessa), 1946, pt. 3, pp. 7-17.

This is an analysis of 250 cases of late sequelae of ocular war injuries treated at the Ukraine Eye Institute for long periods of time, in an effort to exhaust all possible therapeutic procedures for restoration of even a small fraction of visual acuity. Of 64 eyes of 58 patients with traumatic iridocyclitis, 38 had no form vision before the beginning of therapy, 25 had vision from counting fingers to 0.1, and only one eye had a visual acuity above 0.1. Of the 63 patients with vision below 0.1, 29 recovered a visual acuity of 0.1 to 1. Of 21 eyes with imperfect light projection 4 remained unimproved; in 2 eyes vision improved to normal light projection, in 3 to counting of fingers, and in the others to a slight but measurable visual acuity. It is significant that four apparently hopeless eyes in the subatrophic stage showed some improvement.

Twenty patients had profound damage to the vitreous, 14 as a result of a perforating injury, and six after contusion. Eleven eyes had an extensive exudate in the vitreous, which in six encapsulated an intraocular foreign body. Five had a retinal detachment. There was some improvement in 18 of them. The period of observation ranged from six weeks to four years.

Tissue therapy was strikingly effective as a postoperative measure in 26 out of 27 cases of posttraumatic sequelae. Of 67 patients with subatrophic eyes which would usually be enucleated, 32 were freed of invalidism by alternating courses of tissue therapy and surgical procedures.

Ray K. Daily.

Kashuk, M. E. **Therapeutic use of autoclaved preserved tissue in the treatment of sequelae of military ocular injuries.** Oftal. Jour. (Odessa), 1946, pt. 3, pp. 17-20.

This is a report of a clinical investigation on 60 cases of traumatic ocular lesions, treated with implantation of sterilized preserved skin into a subcutaneous pocket behind the ear, and with implantation of sterilized preserved placenta into the subconjunctival sac. This therapeutic pattern had a definitely favorable effect on eyes with traumatic keratitis, traumatic purulent corneal ulcers, traumatic iridocyclitis, resistant to other forms of therapy, traumatic uveitis with vitreous opacities, and traumatic chorioretinitis. In nine out of 12 cases of traumatic optic atrophy visual acuity and the fields improved.

Ray K. Daily.

Khoroshina, A. G. **Treatment of sequelae of ocular war injuries with preserved tissue.** Oftal. Jour. (Odessa), 1946, pt. 3, pp. 21-25.

A detailed analysis is reported of 15 patients treated with tissue therapy. The eyes were injured by mine or bomb explosions. Two eyes were damaged by contusions, and 14 eyes had perforating injuries. Most of these patients had been discharged from other hospitals after all other procedures proved futile. Objective improvement and improved visual acuity was obtained in 12 eyes. In chronic iridocyclitis in subatrophic eyes the photophobia and irritative symptoms disappeared. Corneal leucoma became somewhat less dense, and in one eye a semitransparent transplant became transparent. Vitreous opacities were absorbed, and in optic atrophy the narrow arteries on the disk dilated.

Ray K. Daily.

Levkoieva, E. T. **The regeneration of wounds of external membrane of the eye in the light of new pathologico-anatomical results.** Brit. Jour. Ophth., 1947, v. 31, June, pp. 336-361.

The author has studied sections from 6,000 eyes enucleated over a period of many years.

A clinical diagnosis of endophthalmitis is frequently disproved microscopically. Repeated hemorrhages occurring late are proof of constant irritation resulting from non-closed or badly closed wounds. The healing process and the fate of the perforated eye depends chiefly on the primary surgical treatment.

The author highly recommends direct apposition of wounds, and shows many photomicrographs of poorly approximated wounds when only the conjunctival flap of Kuhnt was used. Conjunctivoplasty closes the superficial layers but the deep edges are not brought into apposition. This encourages the excessive production of fibroblasts which results in a contracted scar, flattening of the wound area and an irritation of the eye, which is often difficult to differentiate clinically from sympathetic ophthalmia. In one clinic, proper suturing of all wounds of the cornea and sclera reduced the frequency of enucleations by 8.9 percent. (14 photomicrographs.) O. H. Ellis.

Paufique, L. **Head of the femur implants after enucleation.** Ann. d'Ocul., 1947, v. 180, March, pp. 129-139.

Inert organic substances which have been used as implants are discussed in detail. The head of the femur of infants that died at the age of three to four months is considered the most desirable implant in Tenon's capsule. After removal, it is immediately placed in 20 percent formalin for eight hours and then in water for four hours. It is then placed successively in 40, 60, and 80 percent solutions of alcohol and at the end of eight hours in 95 percent alcohol. One-half hour before use it is put in normal salt solution. The proximal or spherical surface is forward and the cut end backward. Two catgut sutures are inserted in the anterior surface, one above and the other below the mid-line. The implant is placed in the muscle cone and the muscles sutured over it vertically and horizontally. The implant sutures are tied over the superior and inferior recti tendons. Tenon's capsule and the conjunctiva are sutured over the implant and muscles. The above technique may also be used to improve the appearance of prostheses when simple enucleation had been done. Through a linear undermining incision in the lower conjunctiva the implant is inserted and sutured in position. (24 references.)

Chas. A. Bahn.

Scripchenko, C. P. **Tissue therapy of war invalids.** Oftal. Jour. (Odessa), 1946, pt. 3, pp. 25-29.

The tabulated data of the visual acuity of war-blind persons at the end of the treatment, which consisted of injections of extracts of leaves of aloes preserved in darkness, show definite, if minute improvement. Most responsive to this form of therapy are injuries of the retina and choroid, and the treatment is least effective in methyl alcohol poisoning. Ray K. Daily.

Somerset, E. J. **Foreign body localization: the ring method.** Indian M. Gaz., 1947, v. 82, Feb., pp. 50-53.

An antero-posterior and a lateral X-ray film are taken on which the shadow of the ring will appear as a perfect circle and a line, respectively, if the films are properly placed in relation to the eye. Measurements are taken and transferred to a schematic drawing of the eye. Whatever the magnification of the X ray, the diameter of the ring is known to be 12 mm., and all other measurements can be adjusted by simple calculation. Irwin E. Gaynon.

17

SYSTEMIC DISEASES AND PARASITES

Agundis, Teódulo. **Marfan's syndrome.** Anales de la Soc. Mexicana de Oft., 1947, v. 21, April-June, pp. 113-123.

Two cases encountered personally are recorded by the author. The first was in a young woman who was sent to the ophthalmic service of the City Hospital of San Luis Potosî, with absolute glaucoma of the right eye, the crystalline lens of which was opaque and dislocated up and inward. The left eye had normal tension, but showed a luxation of the lens similar to that of the right eye. There was notable lengthening of the extremities with arachnodactyly. The second patient was a man of 28 years, with lifelong poor vision. The crystalline lenses were displaced upward and outward. The right eye counted fingers at 70 cm., the left at 40 cm. The ophthalmoscopic description of the disc suggests very high astigmatism. The limbs were

notably longer than normal, there was arachnodactyly, and the nails of some fingers were atrophic and corrugated. X-ray examination of the cranium, the hands, and the thorax yielded signs of acromegaly, and also of aortitis and cardiac hypertrophy. (References.)

W. H. Crisp.

Castresana y Guinea, Angel. **Ocular myiasis.** Arch. de la Soc. Oft. Hisp.-Amer., 1947, v. 7, Feb., pp. 163-172.

A case of external ophthalmomyiasis, which is rare in Spain, occurred in a six-year-old child, in whom the larvae of oestrum avis were deposited in the conjunctival sac, while she was at play. A rapid inflammatory reaction of the conjunctiva and cornea ensued, and on examination numerous rapidly motile parasites were found and removed. Two small hemorrhages in the bulbar conjunctiva resulted either from direct trauma by the hooks of the parasite, or from a conjunctival necrosis produced by ferments of the parasite. The literature is reviewed, and the importance of early diagnosis is emphasized. Treatment consists in prompt extraction of the parasites, and the use of mercurial ointments. (2 illustrations.)

Ray K. Daily.

Franceschetti, A., and Bourquin, J. **Rubella during pregnancy and congenital malformation of the infant.** Ann. d'Ocul., 1946, v. 179, Dec., pp. 623-627.

Practically every expectant mother who has rubella during the first part of pregnancy must expect a malformed child. Among 479 infants of mothers that had measles during the first part of pregnancy, that have been reported there were included 274 cases of cataract and other ocular malformations, 52 of microphthalmus, 215 of deafness, and 181 of cardiac malformation. Two types of cataract were observed; one central with transparent periphery and the other total, usually flat and membranous. Fundus pigment changes, especially in the macula, were frequently present. Five additional cases are described.

In pregnant women who have been exposed, immunizing serum should be used. The advisability of therapeutic abortion must be seriously considered.

Chas. A. Bahn.

Givner, I., Bruger, M., and Lowenstein, O. **Exophthalmos and associated ocular disturbances in hyperthyroidism.** Arch. of Ophth., 1947, v. 37, Feb., pp. 211-219. (See Section 13, Eyeball and orbit.)

Grammatico, A. D. **Ophthalmologic contribution to the diagnosis and treatment of headache.** Arch. de Oft. de Buenos Aires, 1946, v. 21, Aug., p. 219.

A chronic headache of many years resulted from vascular instability. The instillation of ergotropyl in the eyes together with thyroid therapy internally and adequate diet brought about a complete cessation of the headaches and a definite enlargement of the visual fields. (Tables, visual field charts, bibliography.)

Plinio Montalván.

Graue, Enrique. **A year in the Xoquiapan leprosarium.** Anales de la Soc. Mexicana de Oft., 1947, v. 21, Jan.-March, pp. 23-30.

As titular ophthalmologist of the "Dr. Pedro López" leprosarium at Xoquiapan, about 22 miles from the City of Mexico, the author has studied the lesions of the disease in various parts of the eye. The usual population of this settlement varies between four and five hundred patients, concen-

trated by the Mexican Department of Public Welfare from various leprogenous zones of the Republic. The cornea is the tissue most frequently affected. The sclera, episclera, and iris follow and are almost alike in frequency of involvement. Some authors even believe that the eye is the usual portal of entry of the disease. W. H. Crisp.

Leriche, Rene. **Surgical treatment of Sjögrens syndrome; the result, after 28 months, of bilateral section of the vertebral nerve.** La Presse Medicale. 1947, no. 7, Feb. 1, pp. 77-78. (See Section 14, Eyelids and lacrimal apparatus.)

Paschkis, K. E., and Cantarow, A. **Hyperophthalmopathic syndrome in thyroid disease.** J. Clin. Endocrin., 1947, v. 7, Feb., pp. 102-114.

The occurrence of proptosis, paresis of external ocular muscles, swelling of the lids, edema of the conjunctiva, and retrobulbar pain in patients with thyroid disease is discussed as the hyperophthalmopathic syndrome. The five case reports demonstrate that the pathologic physiology is not completely understood. Thyroidectomy should be avoided in potential severe ophthalmopathy. Severe ophthalmopathy, far out of proportion to the thyroid toxic manifestations, is a clear contraindication to thyroidectomy.

The effect of iodine should be studied and medication continued to produce the lowest possible basal metabolic rate. Where there is the slightest doubt operation is inadvisable.

The emergency treatment of ophthalmopathy consists of protection of the eyes by local measures followed by decompressing operations. Medical treatment is directed to supression of excessive secretion of the anterior lobe of the pituitary gland. Large doses of estrogenic hormones suppress pituitary function and the secretion of the thyrotropic hormone. Thyroid medication primarily suppresses the thyrotropic hormone. X-ray therapy of the pituitary gland attempts direct suppression of the over-active gland. (3 Figures.)

H. C. Weinberg.

Pedico, O. **Orbital cysticercus.** Rassegna Ital. d'Ottal., 1947, v. 16, March-April, pp. 149-165.

Four stages in the development of the cysticercus which was present in the left orbit of a soldier, are described in detail. First there was slight discomfort and commencing impairment of ocular motility, then exophthalmos with marked chemosis of the conjunctiva, resulting from venous obstruction. In the third stage the tumor was palpable behind and above the globe. A fourth stage has been known, in which involvement of the accessory sinuses, cranial cavity and nasal fossae occur.

Aspiration of the mass gave a limpid fluid, containing hooklets, cells and a di-basic phosphate of calcium.

Eugene M. Blake.

Rosso, Silvio. **The effect of estrogens upon the retinal arterial pressure.** Rassegna Ital. d'Ottal., 1947, v. 16, Jan.-Feb., pp. 3-16.

Rosso studied the retinal arterial pressure in patients with primary amenorrhea, follicular hypersecretion, dysmenorrhea, and normal menopause. After the patient was treated with various natural and synthetic estrogens further pressure readings were made. The estrogens have no effect upon people in hormonal equilibrium or where there is an estrogenic saturation. In primary amenorrhea there ex-

ists a marked sensitivity to the estrogen, which induces a retinal hypotension which lasts from a few hours to exhaustion of the supply of the hormone. (7 tables, 30 references.)

E. M. Blake.

Schmidtke, R. L. **Hypovitaminosis A in ophthalmology.** Arch. of Ophth., 1947, v. 37, May, pp. 653-667.

The author has reviewed the literature of various experiments involving the use of vitamin A in the treatment of ocular diseases. He draws the following conclusions:

1. Hypovitaminosis A may exist in persons who presumably are receiving an adequate diet.

2. Even in the absence of demonstrable ocular lesions, poor dark adaptation is not presumptive evidence of vitamin A deficiency.

3. Fasting vitamin A levels of the blood are of value as a diagnostic aid in establishing the existence of a deficiency.

4. More reports on early ocular changes in vitamin A deficiency need to be made before biomicroscopic examination can be a real diagnostic aid.

5. The corneal and conjunctival lesions in vitamin A deficiency are probably neurotropic and result from degenerative changes in the trigeminal nerve.

6. Keratoconjunctivitis sicca is probably one of the many ways in which vitamin A deficiency manifests itself.

7. Some of the heretofore unexplainable ocular congenital anomalies are undoubtedly due to a vitamin A deficiency in the mother at some critical time during the period of gestation.

8. Vitamin A deficiency may be caused by (a) reduced consumption; (b) defective absorption; (c) uneconomical utilization and (d) excessive utilization (1) during rapid growth, (2) during illnesses or (3) during pregnancy.

9. Parenteral administration of vitamin A is sometimes indicated.

10. Topical application of vitamin A is of doubtful value. (101 references.)

R. W. Danielson.

Solanés, M. P. **The Vogt-Koyanagi syndrome.** Anales de la Soc. Mexicana de Oft., 1947, v. 5, Jan.-March, pp. 12-23. (See Section 7, Uveal tract, sympathetic disease, and aqueous humor.)

Speas, W. P. **Some allergic manifestations of the eye.** N. Carolina M.J., 1947, v. 8, June, pp. 364-366.

The pathologic ocular manifestations of allergy include angioneurotic edema, blepharitis, conjunctivitis, and keratis. Iritis, cyclitis, uveitis, endophthalmitis, and retinitis may follow drug therapy. Cataract, sympathetic ophthalmia and scintillating scotoma also may be induced by sensitivity to one or more offending agents. These may be mineral, vegetable or animal in origin. The diagnosis is made by a careful history, the use of skin tests, conjunctival tests, elimination tests and visits to the patients' environment.

Vernal conjunctivitis, the most common allergic ocular manifestation, occurs in the limbic type which is made up of phlyctenule-like vesicles at the limbus, and the palpebral type characterized by severe and persistent granulomas in the upper lid with a heavy viscid mucous discharge. Itching, lacrimation, redness, edema, scaling, and ulceration of the lids are the most common symptoms.

Treatment consists of removal of the offending allergens or of desensitization. General supportive treatment is advised with the addition of calcium,

histaminase, vitamins, and a salt free diet. Irrigations of the eyes with saline solution and the instillation of vasoconstricting drugs and cold compresses offer comfort to the patient.

H. C. Weinberg.

18

HYGIENE, SOCIOLOGY, EDUCATION AND HISTORY

Alvaro, M. E. **Organized ophthalmology.** Arch. Chilenos de Oft., 1946, v. 2, July-Oct., pp. 219-225.

The author's address emphasizes the educational value of frequent medical meetings for the exchange of ideas and report of special cases. He commends the standardization of hospitals accomplished by the American College of Surgeons, and advises for the South American countries better undergraduate teaching of ophthalmology and more systematic training of those graduates who intend to follow the specialty.

W. H. Crisp.

Arruga, H. **Drawings of the fundus.** Arch. de la Soc. Oft. Hisp.-Amer., 1947, v. 7, Feb., pp. 117-125.

It is pointed out that illustrations convey more vivid impressions than descriptions, and attention is called to the inaccuracies in the size and position of peripheral lesions in drawings, due to the difficulty of transferring impressions of a concave surface to a flat drawing. Arruga uses water colors applied with a brush, and a spray gun. The combined use of the two methods is described in detail and the results illustrated with the beautiful fundus drawings, for which Arruga is well known. (11 illustrations.)

Ray K. Daily.

Cogan, D. G. **Aims and aids in the teaching of basic sciences in ophthalmology.** Arch. of Ophth., 1947, v. 37, April, pp. 428-432.

A basic science course in ophthalmology should aim primarily to lay a foundation for the appreciation of clinical ophthalmology. The course should be taken by a student just prior to his ophthalmic residency if possible, but in any case not during the residency. It is best that the teaching be done by persons who are actively working in the field of ophthalmology. Such persons are to be found almost exclusively in ophthalmic research centers. In so far as there are few ophthalmic centers with personnel trained in basic sciences, the courses, at present, should be given in only a limited number of places. The classes should be sufficiently large, however, to supply the residents for the many clinical institutions which do not have the basic science facilities.

The following subjects are suggested: anatomy, histology and embryology; physical and physiologic optics; physiology and biochemistry; neuroanatomy and neurophysiology; bacteriology; pharmacology and toxicology; ophthalmic instrumentation.

John C. Long.

Heath, Parker. **Medical assistance at professional level.** Amer. Jour., Ophth., 1947, v. 30, August, pp. 992-994.

Lindner, K. **New things in ophthalmology.** Wien. Klin. Wchnschr., 1947, v. 59, May 2, pp. 265-267.

The author reviews recent progress in a postgraduate course. He stresses the importance of the discovery of Ascher that there are vessels near the limbus filled with clear liquid which flow into the neighboring veins. Pressure on the veins fills these vessels and Schlemm's canal with blood. Bailliard's method of measuring the blood pres-

sure in the central retinal artery and the difference between retinal (and intracranial) pressure on one hand and general blood pressure on the other are discussed. Hruby's accessory lens for investigation of the posterior vitreous with the slitlamp is described. Rieken contributed a method to measure adaptation objectively. The sulfonamides and penicillin enlarged our therapeutic possibilities, the former especially against trachoma and gonorrhoic ophthalmia, the latter against gonorrhoea and staphylococcic infections. Serpiginous ulcer is effectively treated by rubbing a 20-percent zinc sulfate solution into the cornea. Lindner successfully used Elliot trephining in serpiginous ulcer. The most frequent surgical intervention against glaucoma now is iridencleisis. Desperate cases may respond to cyclodiathermy of Vogt. Cataract surgery advanced with the development of the intracapsular extraction and corneo-scleral sutures. Early removal of infected lenses after perforating injuries is recommended. Shortening operations by excision or partial excision of the sclera aid in certain cases of detachment. Sato describes a method for improving keratoconus by incising the cornea from behind, followed by pressure bandage. Lindner also discusses his new theory of the development of simple as well as high myopia. He bases his theory on the metabolism of the eye during different working conditions, and especially stresses the importance of the extravasation of a tissue-softening serumprotein. These products of the metabolism may be detrimental to the structures of the suprachoroid and sclera which may also have an inherited anatomical weakness.

Max Hirschfelder.

Mercier, A. **Ophthalmology and av ation.** Arch. d'Opht., 1946, v. 6, no. 4, pp. 413-435.

This report is a review of the relationships between ophthalmology and military and civilian aviation. Among the subjects considered in relation to their function in aviation are visual acuity, visual aptitude, night vision, heterophoria, visual fields, effects of acceleration and deceleration on vision, altitude effects, glare, effect of vibration, and chemical intoxications from gasoline vapors, carbon monoxide, and other poisons.

The author discusses in some detail the visual standards for the various classifications of pilots and observers. The bibliography includes 60 pertinent references covering the entire field of aviation ophthalmology.

Phillips Thygeson.

Onfray, R. **Centenary of Edmond Landolt, founder of the Archives d'Ophtalmologie (1846-1926).** Arch. d'Opht., 1946, v. 6, no. 4, pp. 460-468.

This biographical sketch was inspired by the one hundredth anniversary, on the 17th of May, 1946, of the birth of Aarau Edmond Landolt, one of the great pioneers of ophthalmology. Born in Switzerland, Landolt was the son of a professor of philosophy in a Protestant seminary in Basle. Landolt received his doctorate in medicine from the University of Basle in 1868 and entered Horner's clinic at Zurich the following year. After the War of 1870, in which he took part as a member of the Swiss ambulance service, Landolt studied at Heidelberg with Helmholz, then in Holland with Donders and Snelling. He then migrated to Paris where he very soon became a leader in ophthalmology. In 1882 he founded,

with Panas and Poncet, the Archives d'Ophtalmologie. Author of a great number of ophthalmological studies from 1880 to 1925, he is remembered particularly for the development of numerous optical and surgical instruments and for the surgical treatment of strabismus. He represented the best in French ophthalmology and left an indelible imprint on the science.

Phillips Thygeson.

Roper-Hall, M. J. **Research in Zurich.** Brit. Jour. Ophth., 1947, v. 31, April, pp. 223-228.

The author presents a summary of the work done at Zurich on the pathologic changes in the aqueous humor and the blood-aqueous barrier. Over 1900 anterior chamber punctures were done on normal and diseased eyes. The origin of the cells, increased in inflammation, was proved to be the blood and neighboring tissues. The predominant role of the reticulo-endothelial system in a great number of cases of chronic uveitis was noted. Albumin was increased in proportion to the number of cells, and in chronic inflammations a dissociation between the albumins and the cells was found, comparable to that observed in abnormal cerebrospinal fluid. Cultures were rarely positive even with strongly positive smears, and tubercle bacilli were found in only one case. Organisms found in the anterior chamber in keratitis and anterior uveitis were of etiologic significance.

The permeability of the blood-aqueous wall was studied with the intravenous fluorescein method. Trauma, uveitis, and most general diseases show an increased permeability; however the findings in glaucoma varied. It was found that the fluorescein test showed more minute changes in the permeability of the wall than the Tyndall effect.

O. H. Ellis.

Rusconi, Carlos. **Foramina in the orbital cavity of the pre-Spanish aborigenes of Mendoza.** Arch. de Oft. de Buenos Aires, 1946, v. 21, Aug., p. 202.

The author studied the anatomy of the orbit in 56 skulls of pre-Spanish aborigines of Mendoza, Argentina. Several anatomical variations were found, among them an orbital index of 80 to 108.3, the presence of an infra-orbital plate and a supernumerary supraorbital foramen.

Plinio Montalván.

Sbarski, S. I. **Ocular war injuries in World War II and the organization of special services in the army.** Oftal. Jour. (Odessa), 1946, pt. 3, pp. 36-40.

The following conclusions emerge from an analysis of the ocular injuries in an army hospital for special services. War injuries produce grave ocular damage, and cause blindness in 65 percent of the injured eyes. Surgical procedures at the front comprise closure of the ocular wound, enucleation, and lid repair. The eye service should be organized in connection with other special services, because isolated eye injuries are less frequent than combined injuries. Of the eyes with perforating injuries 40 percent had intraocular foreign bodies, and a powerful magnet is indispensable in an army special hospital.

Ray K. Daily.

Sorsby, Arnold. **Blindness in childhood—past achievements and present problems.** J. Roy. Inst. Publ. Health and Hyg., 1947, v. 10, May, pp. 162-172.

Blindness due to neonatal infection and infectious diseases in early childhood has been reduced from 36.4 per

100,000 to 20.2 per 100,000 over a period of 22 years. This is due to the use of chemotherapy and antibiotics such as the Crédé technique, sulphonamides and penicillin. The passage of a law requiring a report of any purulent infection in a newborn younger than 20 days is also credited with causing this remarkable improvement.

The present problem is to reduce the causes of blindness due to congenital malformations of genetic origin, dietary deficiency in the mother, intrauterine infections, trauma, and also those caused by biochemical changes. Maternal infection has been underestimated and genetic anomalies are also stressed as causes of blindness in early childhood. (3 tables.)

H. C. Weinberg.

19

ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Bein, H. J. **Hereditary aplasia of the optic nerve in mice.** Ophthalmologica, 1947, v. 113, Jan., pp. 12-37.

A famous strain of waltzing mice, kept going by selective breeding, has been under observation at the Department of Anatomy of the University of Basle since 1938. In 1942 the author, in the course of the anatomical examination of an animal from this strain, discovered aplasia of both optic nerves, the chiasm, and both optic tracts. This finding called the author's attention to the occurrence of congenital anomalies of the visual pathway (with or without anomalies of the eyeball or of the ocular adnexa) in waltzing mice. The anatomical findings in three such animals are the basis of the paper under review. Variations as to the degree and extent of the anomaly also occurred. Only a small percentage of the waltzing mice showed gross congenital anomalies of the peripheral or central visual apparatus. The animals with gross anomalies of the visual system did not differ in their behavior from the waltzing animals with normal visual systems. The visually defective ones waltzed with the same endurance, poise and skill as the visually normal animals. Obviously, the congenital anomalies described in the paper did not constitute the specific cause of the waltzing. The presence of congenital visual anomalies could be recognized in vivo by biomicroscopy of the anterior segment of the eye or by ophthalmoscopy. The clinical eye findings will be reported by R. Brueckner. By selective breeding, the author has succeeded in perpetuating the congenital anomaly of the visual system.

Peter C. Kronfeld.

Cooper, E. R. A. **The trochlear nerve in the human embryo and fetus.** Brit. Jour. Ophth., 1947, v. 31, May, pp. 257-275.

In this very comprehensive article, Cooper attempts to answer three puzzling anatomical questions concerning the trochlear nerve. These are: why does the nerve decussate? Why is the decussation on the dorsal aspect of the brain stem? How does the nerve reach the dorsal position where it decussates? The latter two questions are answered while the first remains unanswered. Through well presented microphotographs of serial sections of numerous embryos from 4 mm. (3 to 4 weeks) onward the embryological processes of the nerve and its nucleus are pictured.

The trochlear nucleus originates in series with the oculomotor nucleus but in the basal plate of the isthmus. As the lateral walls of the isthmus link the metencephalic alar to the mesen-

cephalic basal plates, the basal plate of the isthmus becomes compressed until it assumes a position at the ventral extremity of the lateral wall of the isthmus, and it is here that the trochlear nucleus is situated at first. The fibers from the nucleus immediately form a bundle which turns dorsally at once and thus gains an alar situation in the lateral wall of the isthmus caudally to the superior medullary velum where the decussation occurs. The nerve becomes a compact bundle as it leaves its nucleus and remains so; the decussation is a simple crossing of these two bundles and is not an intermingling of the fibers as in the case of the optic nerves. (11 illustrations.)

Morris Kaplan.

Evans, John N. **The capillary sphincter in the human retina.** Arch. of Ophth., 1947, v. 37, Feb., pp. 182-188.

Microscopic studies of surface preparations of retina and choroid showed a peculiar abrupt narrowing of certain capillaries where they joined the vessel of the next larger order. This narrowing is considered to be of a purely histologic nature due to a sphincter-like action in this region. Some capillaries did not show this narrowing.

If retinal and choroidal capillary sphincters do exist, their contraction would have a powerful effect on the capillary bed. It is conceivable that a derangement of this sphincter mechanism by disturbance of the sympathetic hormonal relations might be a factor in producing a type of glaucoma simplex. It might seem reasonable to conclude that the retinal capillary aneurysms associated with glaucoma may have their origin in a prolonged constriction of the sphincter muscle. (4 photomicrographs.) John C. Long.

Gartner, Samuel. **Cyclopia.** Arch. of Ophth., 1947, v. 37, Feb., pp. 220-231.

Cyclopia is a congenital anomaly but is not hereditary, since life is impossible. Its development depends on local factors acting on the midline structures of the face at or before the time of development of the anlagen of the eyes. Two cases of cyclops are reported. In one case the eye was a true single median eye; in the other, a fused double eye. The importance of the pigment epithelium in the development of the choroid, as well as its influence on the retina, is indicated by this study. In both cases the absence of pigment epithelium was associated with almost complete absence of the choroid, the choriocapillaris and the lamina vitrea and by maldevelopment of the overlying retina. In one case a misplaced island of retina was observed buried in the choroid and sclera, in an area where pigment epithelium was lacking. Some proof was found that this anomaly was due to metaplastic development of the pigment epithelium into a retinal type of structure. (14 photographs.)

John C. Long.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
904 Carew Tower, Cincinnati 2

News items should reach the editor by the 12th of the month

DEATHS

Dr. John Conrad Holzberger, Brooklyn, New York, died May 31, 1947, aged 54 years.

Dr. Olaf Martin Steffenson, Chicago, Illinois, died June 3, 1947, aged 68 years.

Dr. George Loring Tobey, Jr., Boston, Massachusetts, died May 20, 1947, aged 65 years.

Dr. Harry W. Woodruff, Joliet, Illinois, died June 20, 1947, aged 79 years.

ANNOUNCEMENTS

EYE LABORATORY FOR LOS ANGELES

The Estelle Doheny Eye Foundation announces the establishment of an eye laboratory located at St. Vincent's Hospital in Los Angeles, designed to provide certain modern ophthalmic facilities badly needed in southern California.

The immediate functions of the laboratory are:

1. To serve as a pathologic laboratory for the diagnosis and registration of pathologic specimens, with preparation of gross specimens and microscopic slides for ophthalmologists submitting specimens, and for the building up of a museum of eye pathology.

2. To serve as a bacteriologic laboratory where diagnostic scrapings, smears, and cultures can be studied, animal inoculations can be made, and the sensitivity of organisms to various drugs and antibiotics can be determined.

3. To provide facilities for fundus, gross, and slitlamp photography, and to maintain a library of photographs and motion pictures for teaching of ophthalmology.

4. To provide an Eye Bank for southern California, with registry of potential donors and recipients. Donor material will be collected, examined, and distributed, and facilities may later be provided for limited instruction in corneal transplant procedures.

5. To distribute and loan certain drugs and equipment that are not otherwise available in the community.

6. To make available certain special equipment for radiation therapy of the eye for use outside the laboratory.

Dr. Alan C. Woods, professor of ophthalmology, Johns Hopkins Medical School; Dr. Cecil O'Brien, professor of ophthalmology, University of Iowa Medical School; and Dr. Phillips Thygeson, formerly professor of ophthalmology, Columbia University, and now associate professor of ophthalmology, University of California, will serve on the advisory board. Dr. A. Ray Irvine, professor of ophthalmology, University of Southern California, will act as chairman of the original board. It is contemplated that the advisory board will also include prominent business and professional leaders as well as representatives from the eye departments of local hospitals, medical schools, and the Eye Section of the Los Angeles County Medical Society.

Dr. Peter Soudakoff, formerly associate professor of ophthalmology at the Peking Union Medical College, will serve as full time pathologist at the laboratory. It is planned that, as part of the residency program of the eye service of the Los Angeles County Hospital and certain local veterans' hospitals, that each resident will spend 2 or 3 months at the laboratory. It is anticipated that a research associate, granted a Fellowship in basic ophthalmic research by the Foundation, will be added to the laboratory staff from time to time.

In creating this perpetual charitable Foundation dedicated to the conservation and restoration of eyesight, Mrs. Edward Laurence Doheny, with great generosity and discerning wisdom, has been careful to insure a flexibility of organization to take care of the immediate practical needs and at the same time provide for eventual development of much needed research in ophthalmology.

GILL HOSPITAL GRADUATE COURSE

The Gill Memorial Eye, Ear, and Throat Hospital, Roanoke, Virginia, announces that its 21st annual spring graduate course in ophthalmology and otolaryngology will be held from April 5 through April 10, 1948.

Among the guest speakers in ophthalmology will be Prof. Adalbert Fuchs, UNRRA-WHO Shanghai, China; Dr. Conrad Berens, New York; Dr. A. D. Ruedemann, Wayne University Medical School, Detroit; Dr. Edwin B. Dunphy, Massachusetts Eye and Ear Infirmary, Boston; Dr. Trygve Gundersen, Boston; Dr. John M. McLean, New York; Dr. Alston Callahan, Medical College of Alabama, Birmingham.

MISCELLANEOUS

DARTMOUTH EYE INSTITUTE CLOSES

The Dartmouth Eye Institute, Hanover, has terminated all clinical activities "because of an inability to provide a sound financial basis for future activities," the managing trustee, John Pearson, has announced. The clinic was es-

tablished in 1921 when Prof. Adelbert Ames, Jr., undertook the study of problems of visual optics. The current work of Professor Ames in visible perception continues under the auspices of the Hanover Institute.

University of Cincinnati appointment

The University of Cincinnati College of Medicine has appointed Dr. Donald J. Lyle professor of ophthalmology and director of the Cincinnati General Hospital's Department of Ophthalmology.

Study of congenital malformations

In an effort to collect more precise data on the relationships between certain maternal infections and congenital malformations, a nationwide study is being sponsored by the American Academy of Pediatrics and the National Society for the Prevention of Blindness. Questionnaires are being sent to obstetricians, ophthalmologists, and pediatricians, seeking the reporting of cases of German measles in expectant mothers and of children with congenital defects that might be attributed to other infections in the expectant mother, such as measles, chicken pox, mumps, and influenza.

Although an association has been established between the occurrence of German measles early in pregnancy and certain congenital defects in the offspring, information is lacking as to the frequency with which this happens and as to the possible influence of other communicable diseases that might have been contracted by the expectant mother.

Data will be studied by the following committee: Dr. Herbert C. Miller, professor of pediatrics, University of Kansas Hospitals, Kansas City, Kansas; Dr. Stewart Clifford and Dr. Clement A. Smith, both of Boston, Massachusetts; Dr. Josef Warkany, of Cincinnati, Ohio; Dr. James Wilson, of Ann Arbor, Michigan; and Dr. Herman Yannet, of Southbury, Connecticut. Physicians knowing of cases are urged to register them with Dr. Miller, chairman of the committee.

Societies

Central Illinois meeting

The eighth meeting of the Central Illinois Society of Ophthalmology and Otolarygology was held at the Abraham Lincoln Hotel, Springfield, Illinois, on August 23rd and 24th. Mr. J. C. Copeland of the Riggs Optical Company, Chicago, gave four talks on: "Practical Session in Retinoscopy," "Practical Applications of the Spherical Equivalent Concept," "Methods of Overcoming Some Difficulties in Cross Cylinder Testing," and "Duochrome Refraction Methods." Other speakers were: Dr. Philip R. McGrath, Peoria, Illinois, who spoke on "Retrobulbar Neuritis;" Dr. French K. Hansel, St. Louis, Missouri, "Allergy in Ophthalmology and Otolaryngology;" and Dr. Carson Gabriel, Quincy, Illinois, "Case Reports: Carcinoma of the Lung and Complete Atelectasis of Lung."

Seminar on industrial vision

A familiarization seminar on Industrial and Occupational Vision will be held the afternoon and evening of November 5, 1947, at the Van Cleve Hotel, Dayton, Ohio. The seminar is being sponsored by Zone 9, Ohio State Optometric Association and the Safety Council, Dayton Chamber of Commerce. The program will include:

2:30 P.M.—Introduction to theme—Occupational Vision; F. E. Billette, O.D., governor, Zone 9; R. N. Roth, O.D., seminar chairman.

3:00 P.M.—Accident Proneness and The Employee's Vision; N. C. Kephart, Ph.D., Assistant professor of Industrial Psychology, Purdue University.

3:30 P.M.—Industry and Seeing—One Aspect of Occupational Seeing; Joseph H. Tiffin, Ph.D., professor of Industrial Psychology, Purdue University.

4:00 P.M.—The Nurse in The Industrial Vision Program—Hazel H. Leedke, R.N., industrial nurse, Health Department, Thilmany Pulp and Paper Company, Kaukauna, Wisconsin.

4:30 P.M.—The Utilization of a Program of Employee Visual Classification, Correction, and Placement Within Our Plant. Richard Wampler, safety director, the Dayton Rubber Manufacturing Company.

5:00 P.M.—Some Aspects of a Plant Safety Goggle Program. William Carroll, director, Industrial Vision Department, White-Haines Optical Company, Columbus, Ohio.

The meeting is open to representatives of industry, and all members of the ophthalmic professions are invited to attend. A registration fee of five dollars per person will include the dinner. For registration write to R. N. Roth, O.D., 2324 Salem Avenue, Dayton 6, Ohio.

Personals

Accepts Yale appointment

Dr. J. Alexander van Heuven, formerly of Utrecht, Holland, has been appointed assistant clinical professor of ophthalmology at the School of Medicine, Yale University. Dr. van Heuven will be associated in private practice with Dr. Eugene M. Blake, head of the department.

Moves to new offices

Dr. Clement C. Clarke announces the removal of his offices to 240 Bradley Street, New Haven 10, Connecticut.

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CHENEY & HUNT, INC.
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J. E. CHENEY & STAFF, INC.
CLARKE, ALBERT L.
THE HARVEY & LEWIS CO.
PHILIP E. MURPHY
Waltham
BENNET R. O'NEIL, OPTICIAN
Woburn
ARTHUR K. SMITH
Worcester
JOHN C. FREEMAN & CO.
THE HARVEY & LEWIS CO.

MINNESOTA
Minneapolis
M. J. CARTER
Rochester
A. A. SCHROEDER
St. Paul
ARTHUR F. WILLIAMS

MISSOURI
Joplin
PHYSICIANS OPTICAL DISPENSARY, INC.
St. Louis
ERKER BROS. OPTICAL CO.
(2 Stores)
GEO. D. FISHER OPTICAL CO.
(2 Stores)
JOHN A. GUHL, INC.

NEW JERSEY
Asbury Park
ANSPACH BROS.
Atlantic City
ATLANTIC OPTICAL CO.
FOERSTER OPTICAL CO.
FREUND BROTHERS
Camden
E. F. BIRBECK CO.
HARRY N. LAYER
J. E. LIMEBURNER CO.
PELOUZE & CAMPBELL
East Orange
ANSPACH BROS.
H. C. DEUCHLER
JAMES J. KEEGAN
Elizabeth
BRUNNER'S
JOHN E. GAVITT
Englewood
HOFFRITZ, FRED G.
Hackensack
HOFFRITZ & PETZOLD
Irvington
LOUIS P. NOSHER, DISPENSING OPTICIAN
Jersey City
WILLIAM H. CLARK
Montclair
STANLEY M. CROWELL CO.
MARSHALL, RALPH E.
Morristown
JOHN L. BROWN
Newark
ANSPACH BROS.
EDWARD ANSPACH
CLINTON OPTICAL SERVICE
KEEGAN, J. J.
MEDICAL TOWER OPTICIANS, INC.
REISS, J. C.
CHARLES STEIGLER
JESS J. WASSERMAN & CO.
Paterson
COLLINS, J. E.
Plainfield
GALL & LEMBKE
LOUIS E. SAFT
Ridgewood
RAY GRIGNON, OPTICIAN
Summit
ANSPACH BROS.
H. C. DEUCHLER
Trenton
GEORGE BRAMMER, OPTICIAN
Union City
ARTHUR VILLAVECCHIA
RICHARD VILLAVECCHIA
Westfield
BRUNNER'S
Wood-Ridge
R. T. KNIERIEM & SON

NEW YORK
Albany
PERRIN & DI NAPOLI
Babylon
PICKUP & BROWN, INC.
Baldwin, L. I.
FRANCIS D. GILLIES
Bronxville
SCHOENIG & CO., INC.
A. R. TRAPP, INC.
Buffalo
BUFFALO OPTICAL CO.
(3 Stores)
FORREST-GOULD OPTICAL CO.
FOX & STANILAND, INC.
(2 Stores)
FRANK & LESSWING OPT. CO.
GIBSON & DOTY
PRECHTEL OPTICAL CO.
PAUL C. RUEHL
SCHLAGER & SCHLAGER
FREDERICK J. TERNHORST
URSIN-SMITH GUILD OPTICIANS
NORMAN E. VANDERCHER
Kenmore
BUFFALO OPTICAL CO.
GIBSON & DOTY
New Rochelle
BATTERSON, INC., JOHN P.
New York City
AITCHISON & CO.
EDWARD J. BOYES
CLAIRMONT & NICHOLS CO.
FRYXELL & HILL
GALL & LEMBKE
HALPERT & FRYXELL, INC.
HARTINGER, EDWARD T.
A. HAUSTETTER, INC.
HOAGLAND, J. S.
LUGENE, INC. (2 Stores)
MARTER & PARSONS
E. B. MEYROWITZ, INC.
(6 Stores)
PAGE & SMITH
H. L. PURDY, INC.
SCHOENIG & CO., INC.
A. R. TRAPP, INC.
Brooklyn
HERBERT E. ALDERMAN, INC.
BADGLEY, H. C.
BECHTOLD & CO., INC.
DOUDIET, ERNEST A.
J. B. HOECKER, INC.
E. B. MEYROWITZ, INC.
J. H. PENNY, INC.
NORTON & SCHNEIDER, INC.
A. M. SHUTT
V. R. TEDESCO
Flushing
BERNARD SHOLKOFF
Garden City
J. H. PENNY CO., INC.
Hempstead
C. WALTER SEE
Jamaica, L. I.
HANSEN, JOHN
Niagara Falls
GEORGE OPTICAL CO.
Rockville Center
SCHOENIG & CO., INC.
Staten Island
VERKUIL BROTHERS
Rochester
WILLIAM J. HICKEY
WALDERT OPTICAL CO.
WHELPLEY & PAUL
Rye
A. E. REYNOLDS
Schenectady
DAY, JAMES E.
OWEN OPTICAL COMPANY
Syracuse
CARPENTER & HUGHES
CLOVER-WHITE OPT. CO.
EDWARD HOMMEL & SONS
Troy
WILLIAMS—OPTICIAN
Utica
KRYSTOL OPTICAL CO.
Watertown
ROBERT L. MEADE
White Plains
CLAIRMONT & NICHOLS CO.
JOSEPH E. KELLY
SAMUEL PEYSER
Yonkers
MILLER & MILLER
PROFESSIONAL OPTICAL SHOP

NORTH CAROLINA
Fayetteville
McBRYDE'S-OPTICIANS

OHIO
Akron
VORWERK PRESCRIPTION OPTICIANS
Cincinnati
ETTER BROTHERS
KOHLER & CO.
SOUTHERN OPTICAL CO.
TOWER OPTICAL CO.
Cleveland
CHARLES F. BANNERMAN
HARRY BRAY OPTICAL CO.
E. B. BROWN OPTICAL CO.
RICHARD H. EBNER
HABERBRACKER OPTICAL CO.
HENRY J. PORTER
REED & McAULIFFE, INC.
Columbus
PHYSICIANS OPTICAL SERVICE
Lakewood
HABERBRACKER OPTICAL CO.
REED & McAULIFFE, INC.
Toledo
PRESTON SADLER

OREGON
Portland
MOOR, HAL. H.

PENNSYLVANIA
Allentown
L. F. GOODIN
Ardmore
WINFIELD DONAT CO.
WALL & OCHS
Bethlehem
PRICE, WILLIAM H.
Bryn Mawr
J. E. LIMEBURNER CO.
Erie
ERIE OPTICAL CO.
HESS BROS.
WILLIAM J. MAGAY CO.
E. K. MEYERS
Homestead
L. E. NEWLAND II, OPTICIAN
Jenkintown
WINFIELD DONAT CO.
J. E. LIMEBURNER CO.
Norristown
J. E. LIMEBURNER CO.
K. E. PALMER
Philadelphia
BENDER & OFF
BONSCHUR & HOLMES, INC.
(2 Stores)
A. W. BRAEUNINGER, INC.
JOHN W. CLEARY
WINFIELD DONAT CO.
(2 Stores)
DOYLE & BOWERS
JOSEPH C. FERGUSON JR., INC.
J. E. LIMEBURNER CO.
(2 Stores)
RALPH H. MACMURTRIE
MAWSON & KIENLE
FRANK A. MORRISON
MULLEN & WOLF
MULLER & FENTON
WILLIAM J. SCOTT, INC.
WILLIAM S. REILLY
THE WM. F. REIMOLO CO.
SIGISMUND
STREET, LINDER & PROFFIT
WALL & OCHS (3 Stores)
WELSH & DAVIS
WILLIAMS, BROWN & EARLE, INC.
JOSEPH ZENTMAYER
Pittsburgh
DAVIDSON & CO.
DUNN-SCOTT CO.
B. K. ELLIOTT CO.
GEO. W. HASS, INC.
F. J. MALONEY
OSCAR P. MATOUS, OPTICIAN
CHARLES F. O'HANLON
SHALER & CRAWFORD, INC.
GEO. B. REED & CO.
HOMER J. SABISH, OPTICIAN
Upper Darby
J. E. LIMEBURNER CO.
West Chester
WINFIELD DONAT CO.
Wilkinsburg
DAVIDSON & CO.

TEXAS
Houston
BARBOUR'S PROFESSIONAL OPTICIANS

VIRGINIA
Lynchburg
BUCKINGHAM & FLIPPIN
A. G. JEFFERSON
Newport News
WHITE OPTICAL CO.
Norfolk
E. E. BURHANS OPTICAL CO.
SMITH & JOHNSON OPTICAL CO., INC.
Portsmouth
JOHNSON OPTICAL CO.

WASHINGTON
Bremerton
WESTERN OPTICAL CO.
Seattle
CHARLES R. OLMSTEAD
WESTERN OPTICAL DISPENSARY
Yakima
PHYSICIANS OPTICAL CO.

WEST VIRGINIA
Charlestown
S. A. AGNEW
Parkersburg
RAWLINGS OPTICIANS, INC.
Wheeling
RAWLINGS OPTICIANS, INC.

CANADA
Hamilton
W. E. DAVIES
Montreal
R. N. TAYLOR & CO., LTD.
Ottawa, Ontario
O. L. DEROUIN
GEO. H. NELMS
SUTHERLAND & PARKIN
Toronto
FRED SHORNEY, LTD.
J. C. WILLIAMS
Winnipeg
RAMSAY, ROBERT S.